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(54) Title: SCHIZOCHYTRIUM PKS GENES

(57) Abstract

The present invention relates to compositions and methods for preparing poly–unsaturated long chain fatty acids in plants, plant parts and plant cells, such as leaves, roots, fruits and seeds. Nucleic acid sequences and constructs encoding PKS–like genes required for the poly–unsaturated long chain fatty acid production, including the genes responsible for eicosapentenoic acid production of *Shewanella putrefaciens* and novel genes associated with the production of docosahexenoic acid in *Vibrio marinus* are used to generate transgenic plants, plant parts and cells which contain and express one or more transgenes encoding one or more of the PKS–like genes associated with such long chain poly–unsaturated fatty acid production. Expression of the PKS–like genes in the plant system permits the large scale production of poly–unsaturated long chain fatty acids such as eicosapentenoic acid and docosahexonoic acid for modification of the fatty acid profile of plants, plant parts and tissues. Manipulation of the fatty acid profiles allows for the production of commercial quantities of novel plant oils and products.

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SCHIZOCHYTRIUM PKS GENES

INTRODUCTION

Field of the Invention

This invention relates to modulating levels of enzymes and/or enzyme components capable of modifying long chain poly-unsaturated fatty acids (PUFAs) in a host cell, and constructs and methods for producing PUFAs in a host cell. The invention is exemplified by production of eicosapentenoic acid (EPA) using genes derived from *Shewanella putrefaciens* and *Vibrio marinus*.

Background

Two main families of poly-unsaturated fatty acids (PUFAs) are the ω3 fatty acids, exemplified by eicosapentenoic acid, and the ω6 fatty acids, exemplified by arachidonic acid. PUFAs are important components of the plasma membrane of the cell, where they can be found in such forms as phospholipids, and also can be found in triglycerides. PUFAs also serve as precursors to other molecules of importance in human beings and animals, including the prostacyclins, leukotrienes and prostaglandins. Long chain PUFAs of importance include docosahexenoic acid (DHA) and eicosapentenoic acid (EPA), which are found primarily in different types of fish oil, gamma-linolenic acid (GLA), which is found in the seeds of a number of plants, including evening primrose (*Oenothera biennis*), borage (*Borago officinalis*) and black currants (*Ribes nigrum*), stearidonic acid (SDA), which is found in marine oils and plant seeds, and arachidonic acid (ARA), which along with GLA is found in filamentous fungi. ARA can be purified from animal tissues including liver and adrenal gland. Several genera of marine bacteria are known which synthesize either EPA or DHA. DHA is present in human milk along with ARA.

PUFAs are necessary for proper development, particularly in the developing infant brain, and for tissue formation and repair. As an example, DHA, is an important constituent of many human cell membranes, in particular nervous cells (gray matter), muscle cells, and spermatozoa and believed to affect the development of brain functions in general and to be essential for the development of eyesight. EPA and DHA have a number of nutritional and pharmacological uses. As an example adults affected by diabetes (especially non insulin-dependent) show

deficiencies and imbalances in their levels of DHA which are believed to contribute to later coronary conditions. Therefore a diet balanced in DHA may be beneficial to diabetics.

For DHA, a number of sources exist for commercial production including a variety of marine organisms, oils obtained from cold water marine fish, and egg yolk fractions. The purification of DHA from fish sources is relatively expensive due to technical difficulties, making DHA expensive and in short supply. In algae such as *Amphidinium* and *Schizochytrium* and marine fungi such as *Thraustochytrium* DHA may represent up to 48% of the fatty acid content of the cell. A few bacteria also are reported to produce DHA. These are generally deep sea bacteria such as *Vibrio marinus*. For ARA, microorganisms including the genera *Mortierella, Entomophthora, Phytium* and *Porphyridium* can be used for commercial production. Commercial sources of SDA include the genera *Trichodesma* and *Echium*. Commercial sources of GLA include evening primrose, black currants and borage. However, there are several disadvantages associated with commercial production of PUFAs from natural sources. Natural sources of PUFA, such as animals and plants, tend to have highly heterogeneous oil compositions. The oils obtained from these sources can require extensive purification to separate out one or more desired PUFA or to produce an oil which is enriched in one or more desired PUFA.

Natural sources also are subject to uncontrollable fluctuations in availability. Fish stocks may undergo natural variation or may be depleted by overfishing. Animal oils, and particularly fish oils, can accumulate environmental pollutants. Weather and disease can cause fluctuation in yields from both fish and plant sources. Cropland available for production of alternate oil-producing crops is subject to competition from the steady expansion of human populations and the associated increased need for food production on the remaining arable land. Crops which do produce PUFAs, such as borage, have not been adapted to commercial growth and may not perform well in monoculture. Growth of such crops is thus not economically competitive where more profitable and better established crops can be grown. Large -scale fermentation of organisms such as *Shewanella* also is expensive. Natural animal tissues contain low amounts of ARA and are difficult to process. Microorganisms such as *Porphyridium* and *Shewanella* are difficult to cultivate on a commercial scale.

Dietary supplements and pharmaceutical formulations containing PUFAs can retain the disadvantages of the PUFA source. Supplements such as fish oil capsules can contain low levels of the particular desired component and thus require large dosages. High dosages result in ingestion of high levels of undesired components, including contaminants. Care must be taken in providing fatty acid supplements, as overaddition may result in suppression of endogenous biosynthetic pathways and lead to competition with other necessary fatty acids in various lipid fractions *in vivo*, leading to undesirable results. For example, Eskimos having a diet high in ω3 fatty acids have an increased tendency to bleed (U.S. Pat. No. 4,874,603). Fish oils have

unpleasant tastes and odors, which may be impossible to economically separate from the desired product, such as a food supplements. Unpleasant tastes and odors of the supplements can make such regimens involving the supplement undesirable and may inhibit compliance by the patient.

A number of enzymes have been identified as being involved in PUFA biosynthesis. Linoleic acid (LA, 18:2 Δ 9, 12) is produced from oleic acid (18:1 Δ9) by a Δ12-desaturase. GLA (18:3 Δ 6, 9, 12) is produced from linoleic acid (LA, 18:2 Δ9, 12) by a Δ6-desaturase. ARA (20:4 Δ 5, 8, 11, 14) is produced from DGLA (20:3 Δ 8, 11, 14), catalyzed by a Δ5-desaturase. Eicosapentenoic acid (EPA) is a 20 carbon, omega 3 fatty acid containing 5 double bonds (Δ 5, 8, 11, 14, 17), all in the *cis* configuration. EPA, and the related DHA (Δ 4, 7, 10, 13, 16, 19, C22:6) are produced from oleic acid by a series of elongation and desaturation reactions. Additionally, an elongase (or elongases) is required to extend the 18 carbon PUFAs out to 20 and 22 carbon chain lengths. However, animals cannot convert oleic acid (18:1 Δ 9) into linoleic acid (18:2 Δ 9, 12). Likewise, μ-linolenic acid (ALA, 18:3 Δ 9, 12, 15) cannot be synthesized by mammals. Other eukaryotes, including fungi and plants, have enzymes which desaturate at positions Δ12 and Δ15. The major poly-unsaturated fatty acids of animals therefore are either derived from diet and/or from desaturation and elongation of linoleic acid (18:2 Δ 9, 12) or μ-linolenic acid (18:3 Δ 9, 12, 15).

Poly-unsaturated fatty acids are considered to be useful for nutritional, pharmaceutical, industrial, and other purposes. An expansive supply of poly-unsaturated fatty acids from natural sources and from chemical synthesis are not sufficient for commercial needs. Because a number of separate desaturase and elongase enzymes are required for fatty acid synthesis from linoleic acid (LA, 18:2 Δ 9, 12), common in most plant species, to the more saturated and longer chain PUFAs, engineering plant host cells for the expression of EPA and DHA may require expression of five or six separate enzyme activities to achieve expression, at least for EPA and DHA, and for production of quantities of such PUFAs additional engineering efforts may be required, for instance the down regulation of enzymes competing for substrate, engineering of higher enzyme activities such as by mutagenesis or targeting of enzymes to plastid organelles. Therefore it is of interest to obtain genetic material involved in PUFA biosynthesis from species that naturally produce these fatty acids and to express the isolated material alone or in combination in a heterologous system which can be manipulated to allow production of commercial quantities of PUFAs.

Relevant Literature

Several genera of marine bacteria have been identified which synthesize either EPA or DHA (DeLong and Yayanos, *Applied and Environmental Microbiology* (1986) 51: 730-737). Researchers of the Sagami Chemical Research Institute have reported EPA production in *E. coli* which have been transformed with a gene cluster from the marine bacterium, *Shewanella*

putrefaciens. A minimum of 5 open reading frames (ORFs) are required for fatty acid synthesis of EPA in *E. coli*. To date, extensive characterization of the functions of the proteins encoded by these genes has not been reported (Yazawa (1996) *Lipids* 31, S-297; WO 93/23545; WO 96/21735).

The protein sequence of open reading frame (ORF) 3 as published by Yazawa, USPN 5,683,898 is not a functional protein. Yazawa defines the protein as initiating at the methionine codon at nucleotides 9016-9014 of the *Shewanella* PKS-like cluster (Genbank accession U73935) and ending at the stop codon at nucleotides 8185-8183 of the *Shewanella* PKS-like cluster. However, when this ORF is expressed under control of a heterologous promoter in an *E. coli* strain containing the entire PKS-like cluster except ORF 3, the recombinant cells do not produce EPA.

Polyketides are secondary metabolites the synthesis of which involves a set of enzymatic reactions analogous to those of fatty acid synthesis (see reviews: Hopwood and Sherman, *Annu. Rev. Genet.* (1990) 24: 37-66, and Katz and Donadio, *in Annual Review of Microbiology* (1993) 47: 875-912). It has been proposed to use polyketide synthases to produce novel antibiotics (Hutchinson and Fujii, *Annual Review of Microbiology* (1995) 49:201-238).

SUMMARY OF THE INVENTION

Novel compositions and methods are provided for preparation of long chain poly-unsaturated fatty acids (PUFAs) using polyketide-like synthesis (PKS-like) genes in plants and plant cells. In contrast to the known and proposed methods for production of PUFAs by means of fatty acid synthesis genes, by the invention constructs and methods are provided for producing PUFAs by utilizing genes of a PKS-like system. The methods involve growing a host cell of interest transformed with an expression cassette functional in the host cell, the expression cassette comprising a transcriptional and translational initiation regulatory region, joined in reading frame 5' to a DNA sequence to a gene or component of a PKS-like system capable of modulating the production of PUFAs (PKS-like gene). An alteration in the PUFA profile of host cells is achieved by expression following introduction of a complete PKS-like system responsible for a PUFA biosynthesis into host cells. The invention finds use for example in the large scale production of DHA and EPA and for modification of the fatty acid profile of host cells and edible plant tissues and/or plant parts.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides designations for the ORFs of the EPA gene cluster of *Shewanella*. Figure 1A shows the organization of the genes; those ORFs essential for EPA production in *E. coli* are numbered. Figure 1B shows the designations given to subclones.

Figure 2 provides the *Shewanella* PKS-like domain structure, motifs and 'Blast' matches of ORF 6 (Figure 2A), ORF 7 (Figure 2B), ORF 8 (Figure 2C), ORF 9 (Figure 2D) and ORF 3 (Figure 2E). Figure 2F shows the structure of the region of the Anabeana chromosome that is related to domains present in *Shewanella* EPA ORFs.

Figure 3 shows results for pantethenylation - ORF 3 in *E. coli* strain SJ16. The image shows [C^{14}] β-Alanine labelled proteins from *E. coli* (strain SJ16) cells transformed with the listed plasmids. Lane 1 represents pUC19, lane 2 represents pPA-NEB (Δ ORF 3), lane 3 represents pAA-Neb (EPA+), lane 4 represents ORF 6 subclone, lane 5 represents ORF 6 + ORF 3 subclones, and lane 6 represents ORF 3 subclone. ACP and an unknown (but previously observed) 35 kD protein were labelled in all of the samples. The high molecular mass proteins detected in lanes 2 and 5 are full-length (largest band) and truncated products of the *Shewanella* ORF-6 gene (confirmed by Western analysis). *E. Coli* strain SJ16 is conditionally blocked in β-alanine synthesis.

Figure 4A shows the DNA sequence (SEQ ID NO:1) for the PKS-like cluster found in *Shewanella*, containing ORF's 3-9. Figure 4B shows the amino acid sequence (SEQ ID NO:2) of ORF 2, which is coded by nucleotides 6121-8103 of the sequence shown in Fig 4A. Figure 4C shows the amino acid sequence (SEQ ID NO:3) of the published, inactive ORF3, translated from the strand complementary to that shown in Figure 4A, nucleotides 9016-8186. Figure 4D shows the nucleotide sequence 8186-9157 (SEQ ID NO:4); its complementary strand codes for ORF 3 active in EPA synthesis. Figures 4E-J show the amino acid sequences (SEQ ID NOS:5-10) corresponding to ORF's 4-9, which are encoded by nucleotides 9681-12590 (SEQ ID NO:81), 13040-13903 (SEQ ID NO:82), 13906-22173 (SEQ ID NO:83), 22203-24515 (SEQ ID NO:84), 24518-30529 (SEQ ID NO:85) and 30730-32358 (SEQ ID NO:86), respectively, of Figure 4A. Figure 4K shows the amino acid sequence (SEQ ID NO:11) corresponding to nucleotides 32834-34327.

Figure 5 shows the sequence (SEQ ID NO:12) for the PKS-like cluster in an approximately 40 kb DNA fragment of *Vibrio marinus*, containing ORFs 6, 7, 8 and 9. The start and last codons for each ORF are as follows: ORF 6: 17394, 25352; ORF 7: 25509, 28160; ORF 8: 28209, 34265; ORF 9: 34454, 36118.

Figure 6 shows the sequence (SEQ ID NO:13) for an approximately 19 kb portion of the PKS-like cluster of Figure 5 which contains the ORFs 6, 7, 8 and 9. The start and last codons for each ORF are as follows: ORF 6: 411, 8369 (SEQ ID NO:77); ORF 7: 8526, 11177 (SEQ ID NO:78); ORF 8: 11226, 17282 (SEQ ID NO:79); ORF 9: 17471, 19135 (SEQ ID NO:80).

Figure 7 shows a comparison of the PKS-like gene clusters of *Shewanella putrefaciens* and *Vibrio marinus*; Figure 7B is the *Vibrio marinus* operon sequence.

Figure 8 is an expanded view of the PKS-like gene cluster portion of *Vibrio marinus* shown in Figure 7B showing that ORFs 6, 7 and 8 are in reading frame 2, while ORF 9 is in reading frame 3.

Figure 9 demonstrates sequence homology of ORF 6 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 6 is depicted on the vertical axis, and the *Vibrio* ORF 6 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity. The repeated lines in the middle correspond to the multiple ACP domains found in ORF 6.

Figure 10 demonstrates sequence homology of ORF 7 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 7 is depicted on the vertical axis, and the *Vibrio* ORF 7 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 11 demonstrates sequence homology of ORF 8 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 8 is depicted on the vertical axis, and the *Vibro*. ORF 8 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 12 demonstrates sequence homology of ORF 9 of *Shewanella putrefaciens* and *Vibrio marinus*. The *Shewanella* ORF 9 is depicted on the vertical axis, and the *Vibrio* ORF 9 is depicted on the horizontal axis. Lines indicate regions of the proteins that have a 60% identity.

Figure 13 is a depiction of various complementation experiments, and resulting PUFA production. On the right, is shown the longest PUFA made in the *E. coli* strain containing the *Vibrio* and *Shewanella* genes depicted on the left. The hollow boxes indicate ORFs from *Shewanella*. The solid boxes indicate ORFs from *Vibrio*.

Figure 14 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Shewanella*, in *E. coli* Fad E-. The chromatogram presents an EPA (20:5) peak.

Figure 15 is a chromatogram showing fatty acid production from complementation of pEPAD8 from *Shewanella* (deletion ORF 8) with ORF 8 from *Vibrio marinus*, in *E. coli* Fad E-. The chromatograph presents EPA (20:5) and DHA (22:6) peaks.

Figure 16 is a table of PUFA values from the ORF 8 complementation experiment, the chromatogram of which is shown in Figure 15.

Figure 17 is a plasmid map showing the elements of pCGN7770.

Figure 18 is a plasmid map showing the elements of pCGN8535.

Figure 19 is a plasmid map showing the elements of pCGN8537.

Figure 20 is a plasmid map showing the elements of pCGN8525.

Figure 21 is a comparison of the *Shewanella* ORFs as defined by Yazawa (1996) <u>supra</u>, and those disclosed in Figure 4. When a protein starting at the leucine (TTG) codon at nucleotides 9157-9155 and ending at the stop codon at nucleotides 8185-8183 is expressed under control of a heterologous promoter in an *E. coli* strain containing the entire PKS-like

cluster except ORF 3, the recombinant cells do produce EPA. Thus, the published protein sequence is likely to be wrong, and the coding sequence for the protein may start at the TTG codon at nucleotides 9157-9155 or the TTG codon at nucleotides 9172-9170. This information is critical to the expression of a functional PKS-like cluster heterologous system.

Figure 22 is a plasmid map showing the elements of pCGN8560.

Figure 23 is plasmid map showing the elements of pCGN8556.

Figure 24 shows the translated DNA sequence (SEQ ID NO:14) upstream of the published ORF 3 and the corresponding amino acids for which they code (SEQ ID NO:15). The ATG start codon at position 9016 is the start codon for the protein described by Yazawa *et al* (1996) *supra*. The other arrows depict TTG or ATT codons that can also serve as start codons in bacteria. When ORF 3 is started from the published ATG codon at 9016, the protein is not functional in making EPA. When ORF 3 is initiated at the TTG codon at position 9157, the protein is capable of facilitating EPA synthesis.

Figure 25 shows the PCR product (SEQ ID NO:16) for SS9 Photobacter using primers in Example 1.

Figure 26 shows probe sequences (SEQ ID NOS:17-31) resulting from PCR with primers presented in Example 1.

Figure 27 shows the nucleotide sequence of *Schizochytrium* EST clones A. LIB 3033-047-B5, LIB3033-046-E6 and a bridging PCR product have now been assembled into a partial cDNA sequence (ORF6 homolog), B. LIB3033-046-D2 (hglc/ORF7/ORF8/ORF9 homolog), C. LIB81-015-D5, LIB81-042-B9 and a bridging PCR product have now been assembled into a partial cDNA sequence (ORF8/ORF9 homolog).

Figure 28 shows a schematic of the similarities between *Shewanella* PKS sequences and *Schizochytrium* sequences.

Figure 29 shows the amino acid sequences inferred from *Schizochytrium* EST clones A. ORF6 homolog, B. hglc/ORF7/ORF8/ORF9 homolog, C. ORF8/ORF9 homolog.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the subject invention, novel DNA sequences, DNA constructs and methods are provided, which include some or all of the polyketide-like synthesis (PKS-like) pathway genes from *Shewanella, Vibrio, Schizochytrium* or other microorganisms, for modifying the poly-unsaturated long chain fatty acid content of host cells, particularly host plant cells. The present invention demonstrates that EPA synthesis genes in *Shewanella putrefaciens* constitute a polyketide-like synthesis pathway. Functions are ascribed to the *Shewanella, Schizochytrium* and *Vibrio* genes and methods are provided for the production of EPA and DHA in host cells. The method includes the step of transforming cells with an expression cassette comprising a DNA encoding a polypeptide capable of increasing the amount of one or more

PUFA in the host cell. Desirably, integration constructs are prepared which provide for integration of the expression cassette into the genome of a host cell. Host cells are manipulated to express a sense or antisense DNA encoding a polypeptide(s) that has PKS-like gene activity. By "PKS-like gene" is intended a polypeptide which is responsible for any one or more of the functions of a PKS-like activity of interest. By "polypeptide" is meant any chain of amino acids, regardless of length or post-translational modification, for example, glycosylation or phosphorylation. Depending upon the nature of the host cell, the substrate(s) for the expressed enzyme may be produced by the host cell or may be exogenously supplied. Of particular interest is the selective control of PUFA production in plant tissues and/or plant parts such as leaves, roots, fruits and seeds. The invention can be used to synthesize EPA, DHA, and other related PUFAs in host cells.

There are many advantages to transgenic production of PUFAs. As an example, in transgenic *E. coli* as in *Shewanella*, EPA accumulates in the phospholipid fraction, specifically in the *sn*-2 position. It may be possible to produce a structured lipid in a desired host cell which differs substantially from that produced in either *Shewanella* or *E. coli*. Additionally transgenic production of PUFAs in particular host cells offers several advantages over purification from natural sources such as fish or plants. In transgenic plants, by utilizing a PKS-like system, fatty acid synthesis of PUFAs is achieved in the cytoplasm by a system which produces the PUFAs through *de novo* production of the fatty acids utilizing malonyl Co-A and acetyl Co-A as substrates. In this fashion, potential problems, such as those associated with substrate competition and diversion of normal products of fatty acid synthesis in a host to PUFA production, are avoided.

Production of fatty acids from recombinant plants provides the ability to alter the naturally occurring plant fatty acid profile by providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs. Production of fatty acids in transgenic plants also offers the advantage that expression of PKS-like genes in particular tissues and/or plant parts means that greatly increased levels of desired PUFAs in those tissues and/or parts can be achieved, making recovery from those tissues more economical. Expression in a plant tissue and/or plant part presents certain efficiencies, particularly where the tissue or part is one which is easily harvested, such as seed, leaves, fruits, flowers, roots, etc. For example, the desired PUFAs can be expressed in seed; methods of isolating seed oils are well established. In addition to providing a source for purification of desired PUFAs, seed oil components can be manipulated through expression of PKS-like genes, either alone or in combination with other genes such as elongases, to provide seed oils having a particular PUFA profile in concentrated form. The concentrated seed oils then can be added to animal milks and/or synthetic or

semisynthetic milks to serve as infant formulas where human nursing is impossible or undesired, or in cases of malnourishment or disease in both adults and infants.

Transgenic microbial production of fatty acids offers the advantages that many microbes are known with greatly simplified oil compositions as compared with those of higher organisms, making purification of desired components easier. Microbial production is not subject to fluctuations caused by external variables such as weather and food supply. Microbially produced oil is substantially free of contamination by environmental pollutants. Additionally, microbes can provide PUFAs in particular forms which may have specific uses. For example, *Spirulina* can provide PUFAs predominantly at the first and third positions of triglycerides; digestion by pancreatic lipases preferentially releases fatty acids from these positions. Following human or animal ingestion of triglycerides derived from *Spirulina*, these PUFAs are released by pancreatic lipases as free fatty acids and thus are directly available, for example, for infant brain development. Additionally, microbial oil production can be manipulated by controlling culture conditions, notably by providing particular substrates for microbially expressed enzymes, or by addition of compounds which suppress undesired biochemical pathways. In addition to these advantages, production of fatty acids from recombinant microbes provides the ability to alter the naturally occurring microbial fatty acid profile by providing new synthetic pathways in the host or by suppressing undesired pathways, thereby increasing levels of desired PUFAs, or conjugated forms thereof, and decreasing levels of undesired PUFAs.

Production of fatty acids in animals also presents several advantages. Expression of desaturase genes in animals can produce greatly increased levels of desired PUFAs in animal tissues, making recovery from those tissues more economical. For example, where the desired PUFAs are expressed in the breast milk of animals, methods of isolating PUFAs from animal milk are well established. In addition to providing a source for purification of desired PUFAs, animal breast milk can be manipulated through expression of desaturase genes, either alone or in combination with other human genes, to provide animal milks with a PUFA composition substantially similar to human breast milk during the different stages of infant development. Humanized animal milks could serve as infant formulas where human nursing is impossible or undesired, or in the cases of malnourishment or disease.

DNAs encoding desired PKS-like genes can be identified in a variety of ways. In one method, a source of a desired PKS-like gene, for example genomic libraries from a *Shewanella, Schizochytrium* or *Vibrio* spp., is screened with detectable enzymatically- or chemically-synthesized probes. Sources of ORFs having PKS-like genes are those organisms which produce a desired PUFA, including DHA-producing or EPA-producing deep sea bacteria growing preferentially under high pressure or at relatively low temperature. Microorgansims such as *Shewanella* which produce EPA or DHA also can be used as a source of PKS-like genes. The probes can be made from DNA, RNA, or non-naturally occurring nucleotides, or mixtures

thereof. Probes can be enzymatically synthesized from DNAs of known PKS-like genes for normal or reduced-stringency hybridization methods. For discussions of nucleic acid probe design and annealing conditions, see, for example, Sambrook *et al*, *Molecular Cloning: A Laboratory Manual* (2[nd] ed.), Vols. 1-3, *Cold Spring Harbor Laboratory*, (1989) or *Current Protocols in Molecular Biology*, F. Ausubel *et al*, ed., Greene Publishing and Wiley-Interscience, New York (1987), each of which is incorporated herein by reference. Techniques for manipulation of nucleic acids encoding PUFA enzymes such as subcloning nucleic acid sequences encoding polypeptides into expression vectors, labelling probes, DNA hybridization, and the like are described generally in Sambrook, *supra*.

Oligonucleotide probes also can be used to screen sources and can be based on sequences of known PKS-like genes, including sequences conserved among known PKS-like genes, or on peptide sequences obtained from a desired purified protein. Oligonucleotide probes based on amino acid sequences can be degenerate to encompass the degeneracy of the genetic code, or can be biased in favor of the preferred codons of the source organism. Alternatively, a desired protein can be entirely sequenced and total synthesis of a DNA encoding that polypeptide performed.

Once the desired DNA has been isolated, it can be sequenced by known methods. It is recognized in the art that such methods are subject to errors, such that multiple sequencing of the same region is routine and is still expected to lead to measurable rates of mistakes in the resulting deduced sequence, particularly in regions having repeated domains, extensive secondary structure, or unusual base compositions, such as regions with high GC base content. When discrepancies arise, resequencing can be done and can employ special methods. Special methods can include altering sequencing conditions by using: different temperatures; different enzymes; proteins which alter the ability of oligonucleotides to form higher order structures; altered nucleotides such as ITP or methylated dGTP; different gel compositions, for example adding formamide; different primers or primers located at different distances from the problem region; or different templates such as single stranded DNAs. Sequencing of mRNA can also be employed.

For the most part, some or all of the coding sequences for the polypeptides having PKS-like gene activity are from a natural source. In some situations, however, it is desirable to modify all or a portion of the codons, for example, to enhance expression, by employing host preferred codons. Host preferred codons can be determined from the codons of highest frequency in the proteins expressed in the largest amount in a particular host species of interest. Thus, the coding sequence for a polypeptide having PKS-like gene activity can be synthesized in whole or in part. All or portions of the DNA also can be synthesized to remove any destabilizing sequences or regions of secondary structure which would be present in the transcribed mRNA. All or portions of the DNA also can be synthesized to alter the base

composition to one more preferable to the desired host cell. Methods for synthesizing sequences and bringing sequences together are well established in the literature. *In vitro* mutagenesis and selection, site-directed mutagenesis, or other means can be employed to obtain mutations of naturally occurring PKS-like genes to produce a polypeptide having PKS-like gene activity *in vivo* with more desirable physical and kinetic parameters for function in the host cell, such as a longer half-life or a higher rate of production of a desired polyunsaturated fatty acid.

Of particular interest are the *Shewanella putrefaciens* ORFs and the corresponding ORFs of *Vibrio marinus* and *Schizochytrium*. The *Shewanella putrefaciens* PKS-like genes can be expressed in transgenic plants to effect biosynthesis of EPA. Other DNAs which are substantially identical in sequence to the *Shewanella putrefaciens* PKS-like genes, or which encode polypeptides which are substantially similar to PKS-like genes of *Shewanella putrefaciens* can be used, such as those identified from *Vibrio marinus* or *Schizochytrium*. By substantially identical in sequence is intended an amino acid sequence or nucleic acid sequence exhibiting in order of increasing preference at least 60%, 80%, 90% or 95% homology to the DNA sequence of the *Shewanella putrefaciens* PKS-like genes or nucleic acid sequences encoding the amino acid sequences for such genes. For polypeptides, the length of comparison sequences generally is at least 16 amino acids, preferably at least 20 amino acids, and most preferably 35 amino acids. For nucleic acids, the length of comparison sequences generally is at least 50 nucleotides, preferably at least 60 nucleotides, and more preferably at least 75 nucleotides, and most preferably, 110 nucleotides.

Homology typically is measured using sequence analysis software, for example, the Sequence Analysis software package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wisconsin 53705, MEGAlign (DNAStar, Inc., 1228 S. Park St., Madison, Wisconsin 53715), and MacVector (Oxford Molecular Group, 2105 S. Bascom Avenue, Suite 200, Campbell, California 95008). BLAST (National Center for Biotechnology Information (WCBI) www.ncbi.nlm.gov; FASTA (Pearson and Lipman, *Science* (1985) 227:1435-1446). Such software matches similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine and leucine; aspartic acid, glutamic acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Substitutions may also be made on the basis of conserved hydrophobicity or hydrophilicity (Kyte and Doolittle, *J. Mol. Biol.* (1982) 157: 105-132), or on the basis of the ability to assume similar polypeptide secondary structure (Chou and Fasman, *Adv. Enzymol.* (1978) 47: 45-148, 1978). A related protein to the probing sequence is identified when $p \geq 0.01$, preferably $p \geq 10^{-7}$ or 10^{-8}.

Encompassed by the present invention are related PKS-like genes from the same or other organisms. Such related PKS-like genes include variants of the disclosed PKS-like ORFs that occur naturally within the same or different species of *Shewanella*, as well as homologues of the disclosed PKS-like genes from other species and evolutionarily related proteins having analogous function and activity. Also included are PKS-like genes which, although not substantially identical to the *Shewanella putrefaciens* PKS-like genes, operate in a similar fashion to produce PUFAs as part of a PKS-like system. Related PKS-like genes can be identified by their ability to function substantially the same as the disclosed PKS-like genes; that is, they can be substituted for corresponding ORFs of *Shewanella*, *Schizochytrium* or *Vibrio* and still effectively produce EPA or DHA. Related PKS-like genes also can be identified by screening sequence databases for sequences homologous to the disclosed PKS-like genes, by hybridization of a probe based on the disclosed PKS-like genes to a library constructed from the source organism, or by RT-PCR using mRNA from the source organism and primers based on the disclosed PKS-like gene. Thus, the phrase "PKS-like genes" refers not only to the nucleotide sequences disclosed herein, but also to other nucleic acids that are allelic or species variants of these nucleotide sequences. It is also understood that these terms include nonnatural mutations introduced by deliberate mutation using recombinant technology such as single site mutation or by excising short sections of DNA open reading frames coding for PUFA enzymes or by substituting new codons or adding new codons. Such minor alterations substantially maintain the immunoidentity of the original expression product and/or its biological activity. The biological properties of the altered PUFA enzymes can be determined by expressing the enzymes in an appropriate cell line and by determining the ability of the enzymes to synthesize PUFAs. Particular enzyme modifications considered minor would include substitution of amino acids of similar chemical properties, e.g., glutamic acid for aspartic acid or glutamine for asparagine.

When utilizing a PUFA PKS-like system from another organism, the regions of a PKS-like gene polypeptide important for PKS-like gene activity can be determined through routine mutagenesis, expression of the resulting mutant polypeptides and determination of their activities. The coding region for the mutants can include deletions, insertions and point mutations, or combinations thereof. A typical functional analysis begins with deletion mutagenesis to determine the N- and C-terminal limits of the protein necessary for function, and then internal deletions, insertions or point mutants are made in the open ready frame to further determine regions necessary for function. Other techniques such as cassette mutagenesis or total synthesis also can be used. Deletion mutagenesis is accomplished, for example, by using exonucleases to sequentially remove the 5' or 3' coding regions. Kits are available for such techniques. After deletion, the coding region is completed by ligating oligonucleotides containing start or stop codons to the deleted coding region after 5' or 3' deletion, respectively.

Alternatively, oligonucleotides encoding start or stop codons are inserted into the coding region by a variety of methods including site-directed mutagenesis, mutagenic PCR or by ligation onto DNA digested at existing restriction sites. Internal deletions can similarly be made through a variety of methods including the use of existing restriction sites in the DNA, by use of mutagenic primers via site directed mutagenesis or mutagenic PCR. Insertions are made through methods such as linker-scanning mutagenesis, site-directed mutagenesis or mutagenic PCR. Point mutations are made through techniques such as site-directed mutagenesis or mutagenic PCR.

Chemical mutagenesis also can be used for identifying regions of a PKS-like gene polypeptide important for activity. A mutated construct is expressed, and the ability of the resulting altered protein to function as a PKS-like gene is assayed. Such structure-function analysis can determine which regions may be deleted, which regions tolerate insertions, and which point mutations allow the mutant protein to function in substantially the same way as the native PKS-like gene. All such mutant proteins and nucleotide sequences encoding them are within the scope of the present invention. EPA is produced in *Shewanella* as the product of a PKS-like system, such that the EPA genes encode components of this system. In *Vibrio*, DHA is produced by a similar system. The enzymes which synthesize these fatty acids are encoded by a cluster of genes which are distinct from the fatty acid synthesis genes encoding the enzymes involved in synthesis of the C16 and C18 fatty acids typically found in bacteria and in plants. As the *Shewanella* EPA genes represent a PKS-like gene cluster, EPA production is, at least to some extent, independent of the typical bacterial type II FAS system. Thus, production of EPA in the cytoplasm of plant cells can be achieved by expression of the PKS-like pathway genes in plant cells under the control of appropriate plant regulatory signals.

EPA production in *E. coli* transformed with the *Shewanella* EPA genes proceeds during anaerobic growth, indicating that O_2-dependent desaturase reactions are not involved. Analyses of the proteins encoded by the ORFs essential for EPA production reveals the presence of domain structures characteristic of PKS-like systems. Fig. 2A shows a summary of the domains, motifs, and also key homologies detected by "BLAST" data bank searches. Because EPA is different from many of the other substances produced by PKS-like pathways, i.e., it contains 5, *cis* double bonds, spaced at 3 carbon intervals along the molecule, a PKS-like system for synthesis of EPA is not expected.

Further, BLAST searches using the domains present in the *Shewanella* EPA ORFs reveal that several are related to proteins encoded by a PKS-like gene cluster found in Anabeana. The structure of that region of the Anabeana chromosome is shown in Fig. 2F. The Anabeana PKS-like genes have been linked to the synthesis of a long-chain (C26), hydroxy-fatty acid found in a glycolipid layer of heterocysts. The EPA protein domains with homology to the Anabeana proteins are indicated in Fig. 2F.

ORF 6 of *Shewanella* contains a KAS domain which includes an active site motif (DXAC*), SEQ ID NO:32, as well as a "GFGG", SEQ ID NO:33, motif which is present at the end of many Type II KAS proteins (see Fig. 2A). Extended motifs are present but not shown here. Next is a malonyl-CoA:ACP acyl transferase (AT) domain. Sequences near the active site motif (GHS*XG), SEQ ID NO:34, suggest it transfers malonate rather than methylmalonate, i.e., it resembles the acetate-like ATs. Following a linker region, there is a cluster of 6 repeating domains, each ~100 amino acids in length, which are homologous to PKS-like ACP sequences. Each contains a pantetheine binding site motif (LGXDS*(L/I)), SEQ ID NOS:35 and 36. The presence of 6 such ACP domains has not been observed previously in fatty acid synthases (FAS) or PKS-like systems. Near the end of the protein is a region which shows homology to ß-keto-ACP reductases (KR). It contains a pyridine nucleotide binding site motif "GXGXX(G/A/P)", SEQ ID NOS:37, 38 and 39.

The *Shewanella* ORF 8 begins with a KAS domain, including active site and ending motifs (Fig. 2C). The best match in the data banks is with the Anabeana HglD. There is also a domain which has sequence homology to the N- terminal one half of the Anabeana HglC. This region also shows weak homology to KAS proteins although it lacks the active site and ending motifs. It has the characteristics of the so-called chain length factors (CLF) of Type II PKS-like systems. ORF 8 appears to direct the production of EPA versus DHA by the PKS-like system. ORF 8 also has two domains with homology to ß-hydroxyacyl-ACP dehydrases (DH). The best match for both domains is with *E. coli* FabA, a bi-functional enzyme which carries out both the dehydrase reaction and an isomerization (*trans* to *cis*) of the resulting double bond. The first DH domain contains both the active site histidine (H) and an adjacent cysteine (C) implicated in FabA catalysis. The second DH domain has the active site H but lacks the adjacent C (Fig. 2C). Blast searches with the second DH domain also show matches to FabZ, a second *E. coli* DH, which does not possess isomerase activity.

The N-terminal half of ORF 7 (Fig. 2B) has no significant matches in the data banks. The best match of the C-terminal half is with a C-terminal portion of the Anabeana HglC. This domain contains an acyl-transferase (AT) motif (GXSXG), SEQ ID NO:40. Comparison of the extended active site sequences, based on the crystal structure of the *E. coli* malonyl-CoA:ACP AT, reveals that ORF 7 lacks two residues essential for exclusion of water from the active site (*E. coli* nomenclature; Q11 and R117). These data suggest that ORF 7 may function as a thioesterase.

ORF 9 (Fig. 2D) is homologous to an ORF of unknown function in the Anabeana Hgl cluster. It also exhibits a very weak homology to NIFA, a regulatory protein in nitrogen fixing bacteria. A regulatory role for the ORF 9 protein has not been excluded. ORF 3 (Fig. 2E) is homologous to the Anabeana HetI as well as EntD from *E. coli* and Sfp of *Bacillus*. Recently, a new enzyme family of phosphopantetheinyl transferases has been identified that includes HetI,

EntD and Sfp (Lamblot RH, *et al.* (1996) A new enzyme superfamily - the phophopantetheinyl transferases. *Chemistry & Biology*, Vol 3, #11, 923-936). The data of Fig. 3 demonstrates that the presence of ORF 3 is required for addition of ß-alanine (i.e. pantetheine) to the ORF 6 protein. Thus, ORF 3 encodes the phosphopantetheinyl transferase specific for the ORF 6 ACP domains. (*See*, Haydock SF *et al.* (1995) Divergent sequence motifs correlated with the substrate specificity of (methyl)malonyl-CoA:acyl carrier protein transacylase domains in modular polyketide synthases, *FEBS Lett.*, 374, 246-248). Malonate is the source of the carbons utilized in the extension reactions of EPA synthesis. Additionally, malonyl-CoA rather than malonyl-ACP is the AT substrate, i.e., the AT region of ORF 6 uses malonyl Co-A.

Once the DNA sequences encoding the PKS-like genes of an organism responsible for PUFA production have been obtained, they are placed in a vector capable of replication in a host cell, or propagated *in vitro* by means of techniques such as PCR or long PCR. Replicating vectors can include plasmids, phage, viruses, cosmids and the like. Desirable vectors include those useful for mutagenesis of the gene of interest or for expression of the gene of interest in host cells. A PUFA synthesis enzyme or a homologous protein can be expressed in a variety of recombinantly engineered cells. Numerous expression systems are available for expression of DNA encoding a PUFA enzyme. The expression of natural or synthetic nucleic acids encoding PUFA enzyme is typically achieved by operably linking the DNA to a promoter (which is either constitutive or inducible) within an expression vector. By expression vector is meant a DNA molecule, linear or circular, that comprises a segment encoding a PUFA enzyme, operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences. An expression vector also may include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors generally are derived from plasmid or viral DNA, and can contain elements of both. The term "operably linked" indicates that the segments are arranged so that they function in concert for their intended purposes, for example, transcription initiates in the promoter and proceeds through the coding segment to the terminator. *See* Sambrook *et al*, *supra*.

The technique of long PCR has made *in vitro* propagation of large constructs possible, so that modifications to the gene of interest, such as mutagenesis or addition of expression signals, and propagation of the resulting constructs can occur entirely *in vitro* without the use of a replicating vector or a host cell. *In vitro* expression can be accomplished, for example, by placing the coding region for the desaturase polypeptide in an expression vector designed for *in vitro* use and adding rabbit reticulocyte lysate and cofactors; labeled amino acids can be incorporated if desired. Such *in vitro* expression vectors may provide some or all of the expression signals necessary in the system used. These methods are well known in the art and the components of the system are commercially available. The reaction mixture can then be

assayed directly for PKS-like enzymes for example by determining their activity, or the synthesized enzyme can be purified and then assayed.

Expression in a host cell can be accomplished in a transient or stable fashion. Transient expression can occur from introduced constructs which contain expression signals functional in the host cell, but which constructs do not replicate and rarely integrate in the host cell, or where the host cell is not proliferating. Transient expression also can be accomplished by inducing the activity of a regulatable promoter operably linked to the gene of interest, although such inducible systems frequently exhibit a low basal level of expression. Stable expression can be achieved by introduction of a nucleic acid construct that can integrate into the host genome or that autonomously replicates in the host cell. Stable expression of the gene of interest can be selected for through the use of a selectable marker located on or transfected with the expression construct, followed by selection for cells expressing the marker. When stable expression results from integration, integration of constructs can occur randomly within the host genome or can be targeted through the use of constructs containing regions of homology with the host genome sufficient to target recombination with the host locus. Where constructs are targeted to an endogenous locus, all or some of the transcriptional and translational regulatory regions can be provided by the endogenous locus. To achieve expression in a host cell, the transformed DNA is operably associated with transcriptional and translational initiation and termination regulatory regions that are functional in the host cell.

Transcriptional and translational initiation and termination regions are derived from a variety of nonexclusive sources, including the DNA to be expressed, genes known or suspected to be capable of expression in the desired system, expression vectors, chemical synthesis The termination region can be derived from the 3' region of the gene from which the initiation region was obtained or from a different gene. A large number of termination regions are known to and have been found to be satisfactory in a variety of hosts from the same and different genera and species. The termination region usually is selected more as a matter of convenience rather than because of any particular property. When expressing more than one PKS-like ORF in the same cell, appropriate regulatory regions and expression methods should be used. Introduced genes can be propagated in the host cell through use of replicating vectors or by integration into the host genome. Where two or more genes are expressed from separate replicating vectors, it is desirable that each vector has a different means of replication. Each introduced construct, whether integrated or not, should have a different means of selection and should lack homology to the other constructs to maintain stable expression and prevent reassortment of elements among constructs. Judicious choices of regulatory regions, selection means and method of propagation of the introduced construct can be experimentally determined so that all introduced genes are expressed at the necessary levels to provide for synthesis of the desired products.

A variety of procaryotic expression systems can be used to express PUFA enzyme. Expression vectors can be constructed which contain a promoter to direct transcription, a ribosome binding site, and a transcriptional terminator. Examples of regulatory regions suitable for this purpose in *E. coli* are the promoter and operator region of the *E. coli* tryptophan biosynthetic pathway as described by Yanofsky (1984) *J. Bacteriol.*, 158:1018-1024 and the leftward promoter of phage lambda (Pλ) as described by Herskowitz and Hagen, (1980) *Ann. Rev. Genet.*, 14:399-445. The inclusion of selection markers in DNA vectors transformed in *E.coli* is also useful. Examples of such markers include genes specifying resistance to ampicillin, tetracycline, or chloramphenicol. Vectors used for expressing foreign genes in bacterial hosts generally will contain a selectable marker, such as a gene for antibiotic resistance, and a promoter which functions in the host cell. Plasmids useful for transforming bacteria include pBR322 (Bolivar, *et al*, (1977) *Gene* 2:95-113), the pUC plasmids (Messing,(1983) *Meth. Enzymol.* 101:20-77, Vieira and Messing, (1982) *Gene* 19:259-268), pCQV2 (Queen, *ibid.*), and derivatives thereof. Plasmids may contain both viral and bacterial elements. Methods for the recovery of the proteins in biologically active form are discussed in U.S. Patent Nos. 4,966,963 and 4,999,422, which are incorporated herein by reference. See Sambrook, *et al* for a description of other prokaryotic expression systems.

For expression in eukaryotes, host cells for use in practicing the present invention include mammalian, avian, plant, insect, and fungal cells. As an example, for plants, the choice of a promoter will depend in part upon whether constitutive or inducible expression is desired and whether it is desirable to produce the PUFAs at a particular stage of plant development and/or in a particular tissue. Considerations for choosing a specific tissue and/or developmental stage for expression of the ORFs may depend on competing substrates or the ability of the host cell to tolerate expression of a particular PUFA. Expression can be targeted to a particular location within a host plant such as seed, leaves, fruits, flowers, and roots, by using specific regulatory sequences, such as those described in USPN 5,463,174, USPN 4,943,674, USPN 5,106,739, USPN 5,175,095, USPN 5,420,034, USPN 5,188,958, and USPN 5,589,379. Where the host cell is a yeast, transcription and translational regions functional in yeast cells are provided, particularly from the host species. The transcriptional initiation regulatory regions can be obtained, for example from genes in the glycolytic pathway, such as alcohol dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase (GPD), phosphoglucoisomerase, phosphoglycerate kinase, etc. or regulatable genes such as acid phosphatase, lactase, metallothionein, glucoamylase, etc. Any one of a number of regulatory sequences can be used in a particular situation, depending upon whether constitutive or induced transcription is desired, the particular efficiency of the promoter in conjunction with the open-reading frame of interest, the ability to join a strong promoter with a control region from a different promoter which allows for inducible transcription, ease of construction, and the like. Of particular interest are promoters

which are activated in the presence of galactose. Galactose-inducible promoters (GAL1, GAL7, and GAL10) have been extensively utilized for high level and regulated expression of protein in yeast (Lue *et al*, (1987) *Mol. Cell. Biol.* 7:3446; Johnston, (1987) *Microbiol. Rev.* 51:458). Transcription from the GAL promoters is activated by the GAL4 protein, which binds to the promoter region and activates transcription when galactose is present. In the absence of galactose, the antagonist GAL80 binds to GAL4 and prevents GAL4 from activating transcription. Addition of galactose prevents GAL80 from inhibiting activation by GAL4. Preferably, the termination region is derived from a yeast gene, particularly *Saccharomyces, Schizosaccharomyces, Candida* or *Kluyveromyces*. The 3' regions of two mammalian genes, γ interferon and $\alpha 2$ interferon, are also known to function in yeast.

Nucleotide sequences surrounding the translational initiation codon ATG have been found to affect expression in yeast cells. If the desired polypeptide is poorly expressed in yeast, the nucleotide sequences of exogenous genes can be modified to include an efficient yeast translation initiation sequence to obtain optimal gene expression. For expression in *Saccharomyces*, this can be done by site-directed mutagenesis of an inefficiently expressed gene by fusing it in-frame to an endogenous *Saccharomyces* gene, preferably a highly expressed gene, such as the lactase gene.

As an alternative to expressing the PKS-like genes in the plant cell cytoplasm, is to target the enzymes to the chloroplast. One method to target proteins to the chloroplast entails use of leader peptides attached to the N-termini of the proteins. Commonly used leader peptides are derived from the small subunit of plant ribulose bis phosphate carboxylase. Leader sequences from other chloroplast proteins may also be used. Another method for targeting proteins to the chloroplast is to transform the chloroplast genome (Stable transformation of chloroplasts of *Chlamydomonas reinhardtii* (1 green alga) using bombardment of recipient cells with high-velocity tungsten microprojectiles coated with foreign DNA has been described. *See*, for example, Blowers *et al Plant Cell* (1989) *1*:123-132 and Debuchy *et al EMBO J* (1989) *8*:2803-2809. The transformation technique, using tungsten microprojectiles, is described by Kline *et al*, *Nature* (London) (1987) *327*:70-73). The most common method of transforming chloroplasts involves using biolistic techniques, but other techniques developed for the purpose may also be used. (Methods for targeting foreign gene products into chloroplasts (Shrier *et al EMBO J.* (1985) *4*:25-32) or mitochondria (Boutry *et al*, *supra*) have been described. *See* also Tomai *et al Gen. Biol. Chem.* (1988) *263*:15104-15109 and US Patent No. 4,940,835 for the use of transit peptides for translocating nuclear gene products into the chloroplast. Methods for directing the transport of proteins to the chloroplast are reviewed in Kenauf *TIBTECH* (1987) *5*:40-47.

For producing PUFAs in avian species and cells, gene transfer can be performed by introducing a nucleic acid sequence encoding a PUFA enzyme into the cells following procedures known in the art. If a transgenic animal is desired, pluripotent stem cells of embryos

can be provided with a vector carrying a PUFA enzyme encoding transgene and developed into adult animal (USPN 5,162,215; Ono *et al.* (1996) *Comparative Biochemistry and Physiology A 113*(3):287-292; WO 9612793; WO 9606160). In most cases, the transgene is modified to express high levels of the PKS-like enzymes in order to increase production of PUFAs. The transgenes can be modified, for example, by providing transcriptional and/or translational regulatory regions that function in avian cells, such as promoters which direct expression in particular tissues and egg parts such as yolk. The gene regulatory regions can be obtained from a variety of sources, including chicken anemia or avian leukosis viruses or avian genes such as a chicken ovalbumin gene.

Production of PUFAs in insect cells can be conducted using baculovirus expression vectors harboring PKS-like transgenes. Baculovirus expression vectors are available from several commercial sources such as Clonetech. Methods for producing hybrid and transgenic strains of algae, such as marine algae, which contain and express a desaturase transgene also are provided. For example, transgenic marine algae can be prepared as described in USPN 5,426,040. As with the other expression systems described above, the timing, extent of expression and activity of the desaturase transgene can be regulated by fitting the polypeptide coding sequence with the appropriate transcriptional and translational regulatory regions selected for a particular use. Of particular interest are promoter regions which can be induced under preselected growth conditions. For example, introduction of temperature sensitive and/or metabolite responsive mutations into the desaturase transgene coding sequences, its regulatory regions, and/or the genome of cells into which the transgene is introduced can be used for this purpose.

The transformed host cell is grown under appropriate conditions adapted for a desired end result. For host cells grown in culture, the conditions are typically optimized to produce the greatest or most economical yield of PUFAs, which relates to the selected desaturase activity. Media conditions which may be optimized include: carbon source, nitrogen source, addition of substrate, final concentration of added substrate, form of substrate added, aerobic or anaerobic growth, growth temperature, inducing agent, induction temperature, growth phase at induction, growth phase at harvest, pH, density, and maintenance of selection. Microorganisms such as yeast, for example, are preferably grown using selected media of interest, which include yeast peptone broth (YPD) and minimal media (contains amino acids, yeast nitrogen base, and ammonium sulfate, and lacks a component for selection, for example uracil). Desirably, substrates to be added are first dissolved in ethanol. Where necessary, expression of the polypeptide of interest may be induced, for example by including or adding galactose to induce expression from a GAL promoter.

When increased expression of the PKS-like gene polypeptide in a host cell which expresses PUFA from a PKS-like system is desired, several methods can be employed.

Additional genes encoding the PKS-like gene polypeptide can be introduced into the host organism. Expression from the native PKS-like gene locus also can be increased through homologous recombination, for example by inserting a stronger promoter into the host genome to cause increased expression, by removing destabilizing sequences from either the mRNA or the encoded protein by deleting that information from the host genome, or by adding stabilizing sequences to the mRNA (*see* USPN 4,910,141 and USPN 5,500,365). Thus, the subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers. Where the subject host is a yeast, four principal types of yeast plasmid vectors can be used: Yeast Integrating plasmids (YIps), Yeast Replicating plasmids (YRps), Yeast Centromere plasmids (YCps), and Yeast Episomal plasmids (YEps). YIps lack a yeast replication origin and must be propagated as integrated elements in the yeast genome. YRps have a chromosomally derived autonomously replicating sequence and are propagated as medium copy number (20 to 40), autonomously replicating, unstably segregating plasmids. YCps have both a replication origin and a centromere sequence and propagate as low copy number (10-20), autonomously replicating, stably segregating plasmids. YEps have an origin of replication from the yeast 2μm plasmid and are propagated as high copy number, autonomously replicating, irregularly segregating plasmids. The presence of the plasmids in yeast can be ensured by maintaining selection for a marker on the plasmid. Of particular interest are the yeast vectors pYES2 (a YEp plasmid available from Invitrogen, confers uracil prototrophy and a GAL1 galactose-inducible promoter for expression), and pYX424 (a YEp plasmid having a constitutive TP1 promoter and conferring leucine prototrophy; (Alber and Kawasaki (1982). *J. Mol. & Appl. Genetics* 1: 419).

The choice of a host cell is influenced in part by the desired PUFA profile of the transgenic cell, and the native profile of the host cell. Even where the host cell expresses PKS-like gene activity for one PUFA, expression of PKS-like genes of another PKS-like system can provide for production of a novel PUFA not produced by the host cell. In particular instances where expression of PKS-like gene activity is coupled with expression of an ORF 8 PKS-like gene of an organism which produces a different PUFA, it can be desirable that the host cell naturally have, or be mutated to have, low PKS-like gene activity for ORF 8. As an example, for production of EPA, the DNA sequence used encodes the polypeptide having PKS-like gene activity of an organism which produces EPA, while for production of DHA, the DNA sequences used are those from an organism which produces DHA. For use in a host cell which already expresses PKS-like gene activity it can be necessary to utilize an expression cassette which provides for overexpression of the desired PKS-like genes alone or with a construct to downregulate the activity of an existing ORF of the existing PKS-like system, such as by antisense or co-suppression. Similarly, a combination of ORFs derived from separate organisms

which produce the same or different PUFAs using PKS-like systems may be used. For instance, the ORF 8 of *Vibrio* directs the expression of DHA in a host cell, even when ORFs 3, 6, 7 and 9 are from *Shewanella*, which produce EPA when coupled to ORF 8 of *Shewanella*. Therefore, for production of eicosapentanoic acid (EPA), the expression cassettes used generally include one or more cassettes which include ORFs 3, 6, 7, 8 and 9 from a PUFA-producing organism such as the marine bacterium *Shewanella putrefaciens* (for EPA production) or *Vibrio marinus* (for DHA production). ORF 8 can be used for induction of DHA production, and ORF 8 of *Vibrio* can be used in conjunction with ORFs 3, 6, 7 and 9 of *Shewanella* to produce DHA. The organization and numbering scheme of the ORFs identified in the *Shewanella* gene cluster are shown in Fig 1A. Maps of several subclones referred to in this study are shown in Fig 1B. For expression of a PKS-like gene polypeptide, transcriptional and translational initiation and termination regions functional in the host cell are operably linked to the DNA encoding the PKS-like gene polypeptide.

Constructs comprising the PKS-like ORFs of interest can be introduced into a host cell by any of a variety of standard techniques, depending in part upon the type of host cell. These techniques include transfection, infection, bolistic impact, electroporation, microinjection, scraping, or any other method which introduces the gene of interest into the host cell (*see* USPN 4,743,548, USPN 4,795,855, USPN 5,068,193, USPN 5,188,958, USPN 5,463,174, USPN 5,565,346 and USPN 5,565,347). Methods of transformation which are used include lithium acetate transformation (*Methods in Enzymology*, (1991) 194:186-187). For convenience, a host cell which has been manipulated by any method to take up a DNA sequence or construct will be referred to as "transformed" or "recombinant" herein. The subject host will have at least have one copy of the expression construct and may have two or more, depending upon whether the gene is integrated into the genome, amplified, or is present on an extrachromosomal element having multiple copy numbers.

For production of PUFAs, depending upon the host cell, the several polypeptides produced by pEPA, ORFs 3, 6, 7, 8 and 9, are introduced as individual expression constructs or can be combined into two or more cassettes which are introduced individually or co-transformed into a host cell. A standard transformation protocol is used. For plants, where less than all PKS-like genes required for PUFA synthesis have been inserted into a single plant, plants containing a complementing gene or genes can be crossed to obtain plants containing a full complement of PKS-like genes to synthesize a desired PUFA.

The PKS-like-mediated production of PUFAs can be performed in either prokaryotic or eukaryotic host cells. The cells can be cultured or formed as part or all of a host organism including an animal. Viruses and bacteriophage also can be used with appropriate cells in the production of PUFAs, particularly for gene transfer, cellular targeting and selection. Any type of plant cell can be used for host cells, including dicotyledonous plants, monocotyledonous plants,

and cereals. Of particular interest are crop plants such as *Brassica*, *Arabidopsis*, soybean, corn, and the like. Prokaryotic cells of interest include *Eschericia, Baccillus, Lactobaccillus, cyanobacteria* and the like. Eukaryotic cells include plant cells, mammalian cells such as those of lactating animals, avian cells such as of chickens, and other cells amenable to genetic manipulation including insect, fungal, and algae cells. Examples of host animals include mice, rats, rabbits, chickens, quail, turkeys, cattle, sheep, pigs, goats, yaks, etc., which are amenable to genetic manipulation and cloning for rapid expansion of a transgene expressing population. For animals, PKS-like transgenes can be adapted for expression in target organelles, tissues and body fluids through modification of the gene regulatory regions. Of particular interest is the production of PUFAs in the breast milk of the host animal.

Examples of host microorganisms include *Saccharomyces cerevisiae*, *Saccharomyces carlsbergensis*, or other yeast such as *Candida, Kluyveromyces* or other fungi, for example, filamentous fungi such as *Aspergillus, Neurospora, Penicillium*, etc. Desirable characteristics of a host microorganism are, for example, that it is genetically well characterized, can be used for high level expression of the product using ultra-high density fermentation, and is on the GRAS (generally recognized as safe) list since the proposed end product is intended for ingestion by humans. Of particular interest is use of a yeast, more particularly baker's yeast (*S. cerevisiae*), as a cell host in the subject invention. Strains of particular interest are SC334 (Mat α pep4-3 prbl-1122 ura3-52 leu2-3, 112 regl-501 gal1; (Hovland *et al* (1989) Gene 83:57-64); BJ1995 (Yeast Genetic Stock Centre, 1021 Donner Laboratory, Berkeley, CA 94720), INVSC1 (Mat α hiw3Δ1 leu2 trp1-289 ura3-52 (Invitrogen, 1600 Faraday Ave., Carlsbad, CA 92008) and INVSC2 (Mat α his3Δ200 ura3-167; (Invitrogen). Bacterial cells also may be used as hosts. This includes *E. coli*, which can be useful in fermentation processes. Alternatively, a host such as a *Lactobacillus* species can be used as a host for introducing the products of the PKS-like pathway into a product such as yogurt.

The transformed host cell can be identified by selection for a marker contained on the introduced construct. Alternatively, a separate marker construct can be introduced with the desired construct, as many transformation techniques introduce multiple DNA molecules into host cells. Typically, transformed hosts are selected for their ability to grow on selective media. Selective media can incorporate an antibiotic or lack a factor necessary for growth of the untransformed host, such as a nutrient or growth factor. An introduced marker gene therefor may confer antibiotic resistance, or encode an essential growth factor or enzyme, and permit growth on selective media when expressed in the transformed host cell. Desirably, resistance to kanamycin and the amino glycoside G418 are of particular interest (*see* USPN 5,034,322). For yeast transformants, any marker that functions in yeast can be used, such as the ability to grow on media lacking uracil, lencine, lysine or tryptophan.

Selection of a transformed host also can occur when the expressed marker protein can be detected, either directly or indirectly. The marker protein can be expressed alone or as a fusion to another protein. The marker protein can be one which is detected by its enzymatic activity; for example ß-galactosidase can convert the substrate X-gal to a colored product, and luciferase can convert luciferin to a light-emitting product. The marker protein can be one which is detected by its light-producing or modifying characteristics; for example, the green fluorescent protein of *Aequorea victoria* fluoresces when illuminated with blue light. Antibodies can be used to detect the marker protein or a molecular tag on, for example, a protein of interest. Cells expressing the marker protein or tag can be selected, for example, visually, or by techniques such as FACS or panning using antibodies.

The PUFAs produced using the subject methods and compositions are found in the host plant tissue and/or plant part as free fatty acids and/or in conjugated forms such as acylglycerols, phospholipids, sulfolipids or glycolipids, and can be extracted from the host cell through a variety of means well-known in the art. Such means include extraction with organic solvents, sonication, supercritical fluid extraction using for example carbon dioxide, and physical means such as presses, or combinations thereof. Of particular interest is extraction with methanol and chloroform. Where appropriate, the aqueous layer can be acidified to protonate negatively charged moieties and thereby increase partitioning of desired products into the organic layer. After extraction, the organic solvents can be removed by evaporation under a stream of nitrogen. When isolated in conjugated forms, the products are enzymatically or chemically cleaved to release the free fatty acid or a less complex conjugate of interest, and are then subjected to further manipulations to produce a desired end product. Desirably, conjugated forms of fatty acids are cleaved with potassium hydroxide.

If further purification is necessary, standard methods can be employed. Such methods include extraction, treatment with urea, fractional crystallization, HPLC, fractional distillation, silica gel chromatography, high speed centrifugation or distillation, or combinations of these techniques. Protection of reactive groups, such as the acid or alkenyl groups, can be done at any step through known techniques, for example alkylation or iodination. Methods used include methylation of the fatty acids to produce methyl esters. Similarly, protecting groups can be removed at any step. Desirably, purification of fractions containing DHA and EPA is accomplished by treatment with urea and/or fractional distillation.

The uses of the subject invention are several. Probes based on the DNAs of the present invention find use in methods for isolating related molecules or in methods to detect organisms expressing PKS-like genes. When used as probes, the DNAs or oligonucleotides need to be detectable. This is usually accomplished by attaching a label either at an internal site, for example via incorporation of a modified residue, or at the 5' or 3' terminus. Such labels can be directly detectable, can bind to a secondary molecule that is detectably labeled, or can bind to an

unlabelled secondary molecule and a detectably labeled tertiary molecule; this process can be extended as long as is practicable to achieve a satisfactorily detectable signal without unacceptable levels of background signal. Secondary, tertiary, or bridging systems can include use of antibodies directed against any other molecule, including labels or other antibodies, or can involve any molecules which bind to each other, for example a biotin-streptavidin/avidin system. Detectable labels typically include radioactive isotopes, molecules which chemically or enzymatically produce or alter light, enzymes which produce detectable reaction products, magnetic molecules, fluorescent molecules or molecules whose fluorescence or light-emitting characteristics change upon binding. Examples of labelling methods can be found in USPN 5,011,770. Alternatively, the binding of target molecules can be directly detected by measuring the change in heat of solution on binding of a probe to a target via isothermal titration calorimetry, or by coating the probe or target on a surface and detecting the change in scattering of light from the surface produced by binding of a target or a probe, respectively, is done with the BIAcore system.

PUFAs produced by recombinant means find applications in a wide variety of areas. Supplementation of humans or animals with PUFAs in various forms can result in increased levels not only of the added PUFAs, but of their metabolic progeny as well. Complex regulatory mechanisms can make it desirable to combine various PUFAs, or to add different conjugates of PUFAs, in order to prevent, control or overcome such mechanisms to achieve the desired levels of specific PUFAs in an individual. In the present case, expression of PKS-like gene genes, or antisense PKS-like gene transcripts, can alter the levels of specific PUFAs, or derivatives thereof, found in plant parts and/or plant tissues. The PKS-like gene polypeptide coding region is expressed either by itself or with other genes, in order to produce tissues and/or plant parts containing higher proportions of desired PUFAs or containing a PUFA composition which more closely resembles that of human breast milk (Prieto *et al.*, PCT publication WO 95/24494) than does the unmodified tissues and/or plant parts.

PUFAs, or derivatives thereof, made by the disclosed method can be used as dietary supplements for patients undergoing intravenous feeding or for preventing or treating malnutrition. For dietary supplementation, the purified PUFAs, or derivatives thereof, can be incorporated into cooking oils, fats or margarines formulated so that in normal use the recipient receives a desired amount of PUFA. The PUFAs also can be incorporated into infant formulas, nutritional supplements or other food products, and find use as anti-inflammatory or cholesterol lowering agents.

Particular fatty acids such as EPA can be used to alter the composition of infant formulas to better replicate the PUFA composition of human breast milk. The predominant triglyceride in human milk is reported to be 1,3-di-oleoyl-2-palmitoyl, with 2-palmitoyl glycerides reported as better absorbed than 2-oleoyl or 2-lineoyl glycerides (*see* USPN 4,876,107). Typically, human

breast milk has a fatty acid profile comprising from about 0.15 % to about 0.36 % as DHA, from about 0.03 % to about 0.13 % as EPA, from about 0.30 % to about 0.88 % as ARA, from about 0.22 % to about 0.67 % as DGLA, and from about 0.27 % to about 1.04 % as GLA. A preferred ratio of GLA:DGLA:ARA in infant formulas is from about 1:1:4 to about 1:1:1, respectively. Amounts of oils providing these ratios of PUFA can be determined without undue experimentation by one of skill in the art. PUFAs, or host cells containing them, also can be used as animal food supplements to alter an animal's tissue or milk fatty acid composition to one more desirable for human or animal consumption.

For pharmaceutical use (human or veterinary), the compositions generally are administered orally but can be administered by any route by which they may be successfully absorbed, e.g., parenterally (i.e. subcutaneously, intramuscularly or intravenously), rectally or vaginally or topically, for example, as a skin ointment or lotion. Where available, gelatin capsules are the preferred form of oral administration. Dietary supplementation as set forth above also can provide an oral route of administration. The unsaturated acids of the present invention can be administered in conjugated forms, or as salts, esters, amides or prodrugs of the fatty acids. Any pharmaceutically acceptable salt is encompassed by the present invention; especially preferred are the sodium, potassium or lithium salts. Also encompassed are the N-alkylpolyhydroxamine salts, such as N-methyl glucamine, described in PCT publication WO 96/33155. Preferred esters are the ethyl esters.

The PUFAs of the present invention can be administered alone or in combination with a pharmaceutically acceptable carrier or excipient. As solid salts, the PUFAs can also be administered in tablet form. For intravenous administration, the PUFAs or derivatives thereof can be incorporated into commercial formulations such as Intralipids. Where desired, the individual components of formulations can be individually provided in kit form, for single or multiple use. A typical dosage of a particular fatty acid is from 0.1 mg to 20 g, or even 100 g daily, and is preferably from 10 mg to 1, 2, 5 or 10 g daily as required, or molar equivalent amounts of derivative forms thereof. Parenteral nutrition compositions comprising from about 2 to about 30 weight percent fatty acids calculated as triglycerides are encompassed by the present invention. Other vitamins, and particularly fat-soluble vitamins such as vitamin A, D, E and L-carnitine optionally can be included. Where desired, a preservative such as a tocopherol can be added, typically at about 0.1% by weight.

The following examples are presented by way of illustration, not of limitation.

EXAMPLES

Example 1

The Identity of ORFs Derived from *Vibrio marinus*

Using polymerase chain reaction (PCR) with primers based on ORF 6 of *Shewanella* (Sp ORF 6) sequences (FW 5' primers CUACUACUACUACCAAGCT AAAGCACTTAACCGTG, SEQ ID NO:41, and CUACUACUACUAACAGCGAAATG CTTATCAAG, SEQ ID NO:42, for *Vibrio* and SS9 respectively and 3' BW primers: CAUCAUCAUCAUGCGACCAAAACCAAATGAGCTAATAC, SEQ ID NO:43, for both *Vibrio* and SS9) and genomic DNAs templates from *Vibrio* and a borophyllic *photobacter* producing EPA (provided by Dr. Bartlett, UC San Diego), resulted in PCR products of *ca.*400 bases for *Vibrio marinus* (*Vibrio*) and *ca.*900 bases for SS9 presenting more than 75% homology with corresponding fragments of Sp ORF 6 (*see* Figure 25) as determined by direct counting of homologous amino acids.

A *Vibrio* cosmid library was then prepared and using the *Vibrio* ORF 6 PCR product as a probe (*see* Figure 26); clones containing at least ORF 6 were selected by colony hybridization.

Through additional sequences of the selected cosmids such as cosmid #9 and cosmid #21, a *Vibrio* cluster (Figure 5) with ORFs homologous to, and organized in the same sequential order (ORFs 6-9) as ORFs 6-9 of *Shewanella*, was obtained (Figure 7). The *Vibrio* ORFs from this sequence are found at 17394 to 36115 and comprehend ORFs 6-9.

Table

Vibrio operon figures

17394 to 25349	length = 7956 nt
25509 to 28157	length = 2649 nt
28209 to 34262	length = 6054 nt
34454 to 36115	length = 1662 nt

The ORF designations for the *Shewanella* genes are based on those disclosed in Figure 4, and differ from those published for the *Shewanella* cluster (Yazawa *et al*, USPN 5,683,898). For instance, ORF 3 of Figure 4 is read in the opposite direction from the other ORFs and is not disclosed in Yazawa *et al* USPN 5,683,898 (See Fig. 24) for comparison with Yazawa *et al* USPN 5,683,898.

Sequences homologous to ORF 3, were not found in the proximity of ORF 6 (17000 bases upstream of ORF 6) or of ORF 9 (*ca.*4000 bases downstream of ORF 9). Motifs characteristic of phosphopantethenyl transferases (Lambalot *et al* (1996) *Current Biology* 3:923-

936) were absent from the *Vibrio* sequences screened for these motifs. In addition, there was no match to Sp ORF 3 derived probes in genomic digests of *Vibrio* and of SC2A *Shewanella* (another bacterium provided by the University of San Diego and also capable of producing EPA). Although ORF 3 may exist in *Vibrio*, its DNA may not be homologous to that of Sp ORF 3 and/or could be located in portions of the genome that were not sequenced.

Figure 6 provides the sequence of an approximately 19 kb *Vibrio* clone comprising ORFs 6-9. Figures 7 and 8 compare the gene cluster organizations of the PKS-like systems of *Vibrio marinus* and *Shewanella putrefacians*. Figures 9 through 12 show the levels of sequence homology between the corresponding ORFs 6, 7, 8 and 9, respectively.

Example 2
ORF 8 Directs DHA Production

As described in example 1, DNA homologous to *Sp* ORF 6 was found in an unrelated species, SS9 *Photobacter*, which also is capable of producing EPA. Additionally, ORFs homologous to *Sp* ORF 6-9 were found in the DHA producing V*brio marinus* (*Vibrio*). From these ORFs a series of experiments was designed in which deletions in each of *Sp* ORFs 6-9 that suppressed EPA synthesis in *E. coli* (Yazawa (1996) *supra*) were complemented by the corresponding homologous genes from *Vibrio*.

The *Sp* EPA cluster was used to determine if any of the *Vibrio* ORFs 6-9 was responsible for the production of DHA. Deletion mutants provided for each of the *Sp* ORFs are EPA and DHA null. Each deletion was then complemented by the corresponding *Vibrio* ORF expressed behind a *lac* promoter.(Figure 13).

The complementation of a *Sp* ORF 6 deletion by a *Vibrio* ORF 6 reestablished the production of EPA. Similar results were obtained by complementing the *Sp* ORF 7 and ORF 9 deletions. By contrast, the complementation of a *Sp* ORF 8 deletion resulted in the production of C22:6. *Vibrio* ORF 8 therefore appears to be a key element in the synthesis of DHA. Figures 14 and 15 show chromatograms of fatty acid profiles from the respective complementations of Sp del ORF 6 with *Vibrio* ORF 6 (EPA and no DHA) and *Sp* del ORF 8 with *Vibrio* ORF 8 (DHA). Figure 16 shows the fatty acid percentages for the ORF 8 complementation, again demonstrating that ORF 8 is responsible for DHA production.

These data show that polyketide-like synthesis genes with related or similar ORFs can be combined and expressed in a heterologous system and used to produce a distinct PUFA species in the host system, and that ORF 8 has a role in determining the ultimate chain length. The *Vibrio* ORFs 6, 7, 8, and 9 reestablish EPA synthesis. In the case of *Vibrio* ORF 8, DHA is also present (*ca.* 0.7%) along with EPA (*ca.* 0.6%) indicating that this gene plays a significant role in directing synthesis of DHA *vs* EPA for these systems.

Example 3

Requirements for Production of DHA

To determine how *Vibrio* ORFs of the cluster ORF 6-9 are used in combination with *Vibrio* ORF 8, some combinations of *Vibrio* ORF 8 with some or all of the other *Vibrio* ORFS 6-9 cluster were created to explain the synthesis of DHA.

Vibrio ORFs 6-9 were complemented with *Sp* ORF 3. The results of this complementation are presented in Figures 16b and 16c. The significant amounts of DHA measured (greater than about 9%) and the absence of EPA suggest that no ORFs other than those of *Vibrio* ORFs 6-9 are required for DHA synthesis when combined with *Sp* ORF 3. This suggests that *Sp* ORF 3 plays a general function in the synthesis of bacterial PUFAs.

With respect to the DHA vs EPA production, it may be necessary to combine *Vibrio* ORF 8 with other *Vibrio* ORFs of the 6-9 cluster in order to specifically produce DHA. The roles of *Vibrio* ORF 9 and each of the combinations of *Vibrio* ORFs (6,8), (7, 8), (8, 9), etc in the synthesis of DHA are being studied.

Example 4

Plant Expression Constructs

A cloning vector with very few restriction sites was designed to facilitate the cloning of large fragments and their subsequent manipulation. An adapter was assembled by annealing oligonucleotides with the sequences AAGCCCGGGCTT, SEQ ID NO:44, and GTACAAGCCCGGGCTTAGCT, SEQ ID NO:45. This adapter was ligated to the vector pBluescript II SK+ (Stratagene) after digestion of the vector with the restriction endonucleases *Asp*718 and *Sst*I. The resulting vector, pCGN7769 had a single *Srf*I (and embedded *Sma*I) cloning site for the cloning of blunt ended DNA fragments.

A plasmid containing the napin cassette from pCGN3223, (USPN 5,639,790) was modified to make it more useful for cloning large DNA fragments containing multiple restriction sites, and to allow the cloning of multiple napin fusion genes into plant binary transformation vectors. An adapter comprised of the self annealed oligonucleotide of sequence CGCGATTTAAATGGCGCGCCCTGCAGGCGGCCGCCTGCAGGGCGC GCCATTTAAAT, SEQ ID NO:46, was ligated into the vector pBC SK+ (Stratagene) after digestion of the vector with the restriction endonuclease *Bss*HII to construct vector pCGN7765. Plamids pCGN3223 and pCGN7765 were digested with *Not*I and ligated together. The resultant vector, pCGN7770 (Figure 17), contains the pCGN7765 backbone and the napin seed specific expression cassette from pCGN3223.

Shewanella constructs

Genes encoding the *Shewanella* proteins were mutagenized to introduce suitable cloning sites 5' and 3' ORFs using PCR. The template for the PCR reactions was DNA of the cosmid pEPA (Yazawa *et al, supra)*. PCR reactions were performed using Pfu DNA polymerase according to the manufacturers' protocols. The PCR products were cloned into *SrfI* digested pCGN7769. The primers CTGCAGCTCGAGACAATGTTGATT TCCTTATACTTCTGTCC, SEQ ID NO:47, and GGATCCAGATCTCTAGCTAGTC TTAGCTGAAGCTCGA, SEQ ID NO:48, were used to amplify ORF 3, and to generate plasmid pCGN8520. The primers TCTAGACTCGAGACAATGAGCCAGACCTC TAAACCTACA, SEQ ID NO:49, and CCCGGGCTCGAGCTAATTCGCCTCACTGTC GTTTGCT, SEQ ID NO:50, were used to amplify ORF 6, and generate plasmid pCGN7776. The primers GAATTCCTCGAGACAATGCCGCTGCGCATCG CACTTATC, SEQ ID NO: 51, and GGTACCAGATCTTTAGACTTCCCCTTGAAG TAAATGG, SEQ ID NO:52, were used to amplify ORF 7, and generate plasmid pCGN7771. The primers GAATTCGTCGACACAATGTCATTACCAGACAATGC TTCT, SEQ ID NO:53, and TCTAGAGTCGACTTATACAGATTCTTCGATGCT GATAG, SEQ ID NO:54, were used to amplify ORF 8, and generate plasmid pCGN7775. The primers GAATTCGTCGACACAATGAATCCTACAGCAACTAACGAA, SEQ ID NO:55, and TCTAGAGGATCCTTAGGCCATTCTTTGGTTTGGCTTC, SEQ ID NO:56, were used to amplify ORF 9, and generate plasmid pCGN7773.

The integrity of the PCR products was verified by DNA sequencing of the inserts of pCGN7771, PCGN8520, and pCGN7773. ORF 6 and ORF 8 were quite large in size. In order to avoid sequencing the entire clones, the center portions of the ORFs were replaced with restriction fragments of pEPA. The 6.6 kilobase *PacI*/*Bam*HI fragment of pEPA containing the central portion of ORF 6 was ligated into *PacI*/*Bam*HI digested pCGN7776 to yield pCGN7776B4. The 4.4 kilobase *Bam*HI/*BglII* fragment of pEPA containing the central portion of ORF 8 was ligated into *Bam*HI/*BglII* digested pCGN7775 to yield pCGN7775A. The regions flanking the pEPA fragment and the cloning junctions were verified by DNA sequencing.

Plasmid pCGN7771 was cut with *XhoI* and *BglII* and ligated to pCGN7770 after digestion with *SalI* and BglII. The resultant napin/ORF 7 gene fusion plasmid was designated pCGN7783. Plasmid pCGN8520 was cut with *XhoI* and *BglII* and ligated to pCGN7770 after digestion with *SalI* and *BglII*. The resultant napin/ORF 3 gene fusion plasmid was designated pCGN8528. Plasmid pCGN7773 was cut with *SalI* and *Bam*HI and ligated to pCGN7770 after digestion with *SalI* and *BglII*. The resultant napin/ORF 9 gene fusion plasmid was designated pCGN7785. Plasmid pCGN7775A was cut with *SalI* and ligated to pCGN7770 after digestion with *SalI*. The resultant napin/ORF 8 gene fusion plasmid was designated pCGN7782. Plasmid pCGN7776B4 was cut with *XhoI* and ligated to pCGN7770 after digestion with *SalI*. The resultant napin/ORF 6 gene fusion plasmid was designated pCGN7786B4.

A binary vector for plant transformation, pCGN5139, was constructed from pCGN1558 (McBride and Summerfelt (1990) *Plant Molecular Biology*, 14:269-276). The polylinker of pCGN1558 was replaced as a *Hin*dIII/*Asp*718 fragment with a polylinker containing unique restriction endonuclease sites, *Asc*I, *Pac*I, *Xba*I, *Swa*I, *Bam*HI, and *Not*I. The *Asp*718 and *Hin*dIII restriction endonuclease sites are retained in pCGN5139. PCGN5139 was digested with *Not*I and ligated with *Not*I digested pCGN7786B4. The resultant binary vector containing the napin/ORF 6 gene fusion was designated pCGN8533. Plasmid pCGN8533 was digested with *Sse*8387I and ligated with *Sse*8387I digested pCGN7782. The resultant binary vector containing the napin/ORF 6 gene fusion and the napin/ORF 8 gene fusion was designated pCGN8535 (Figure 18).

The plant binary transformation vector, pCGN5139, was digested with *Asp*718 and ligated with *Asp*718 digested pCGN8528. The resultant binary vector containing the napin/ORF 3 gene fusion was designated pCGN8532. Plasmid pCGN8532 was digested with *Not*I and ligated with *Not*I digested pCGN7783. The resultant binary vector containing the napin/ORF 3 gene fusion and the napin/ORF 7 gene fusion was designated pCGN8534. Plasmid pCGN8534 was digested with *Sse*8387I and ligated with *Sse*8387I digested pCGN7785. The resultant binary vector containing the napin/ORF 3 gene fusion, the napin/ORF 7 gene fusion and the napin/ORF 9 gene fusion was designated pCGN8537 (Figure 19).

<u>*Vibrio* constructs</u>

The *Vibrio* ORFs for plant expression were all obtained using *Vibrio* cosmid #9 as a starting molecule. *Vibrio* cosmid #9 was one of the cosmids isolated from the *Vibrio* cosmid library using the *Vibrio* ORF 6 PCR product described in Example 1.

A gene encoding *Vibrio* ORF 7 (Figure 6) was mutagenized to introduce a *Sal*I site upstream of the open reading frame and *Bam*HI site downstream of the open reading frame using the PCR primers: TCTAGAGTCGACACAATGGCGGAATTAGCTG TTATTGGT, SEQ ID NO:57, and GTCGACGGATCCCTATTTGTTCGTGTTTGCTA TATG, SEQ ID NO:58. A gene encoding *Vibrio* ORF 9 (Figure 6) was mutagenized to introduce a *Bam*HI site upstream of the open reading frame and an *Xho*HI site downstream of the open reading frame using the PCR primers: GTCGACGGATCCA CAATGAATATAGTAAGTAATCATTCGGCA, SEQ ID NO:59, and GTCGACCTC GAGTTAATCACTCGTACGATAACTTGCC, SEQ ID NO:60. The restriction sites were introduced using PCR, and the integrity of the mutagenized plasmids was verified by DNA sequence. The *Vibrio* ORF 7 gene was cloned as a *Sal*I-*Bam*HI fragment into the napin cassette of *Sal-Bgl*I digested pCGN7770 (Figure 17) to yield pCGN8539. The *Vibrio* ORF 9 gene was cloned as a *Sal*I-*Bam*HI fragment into the napin cassette of *Sal-Bal*I digested pCGN7770 (Figure 17) to yield pCGN8543.

Genes encoding the *Vibrio* ORF 6 and ORF 8 were mutagenized to introduce *Sal*I sites flanking the open reading frames. The *Sal*I sites flanking ORF 6 were introduced using PCR. The primers used were: CCCGGGTCGACACAATGGCTAAAAAGAACA CCACATCGA, SEQ ID NO:61, and CCCGGGTCGACTCATGACATATCGTTCAAA ATGTCACTGA, SEQ ID NO:62. The central 7.3 kb *Bam*HI-*Xho*I fragment of the PCR product was replaced with the corresponding fragment from *Vibrio* cosmid #9. The mutagenized ORF 6 were cloned into the *Sal*I site of the napin cassette of pCGN7770 to yield plasmid pCGN8554.

The mutagenesis of ORF 8 used a different strategy. A *Bam*HI fragment containing ORF 8 was subcloned into plasmid pHC79 to yield cosmid #9". A *Sal*I site upstream of the coding region was introduced on and adapter comprised of the oligonucleotides TCGACATGGAAAATATTGCAGTAGTAGGTATTGCTAATTT GTTC, SEQ ID NO:63, and CCGGGAACAAATTAGCAATACCTACTACTGCAAT ATTTTCCATG, SEQ ID NO:64. The adapter was ligated to cosmid #9" after digestion with *Sal*I and *Xma*I. A *Sal*I site was introduced downstream of the stop codon by using PCR for mutagenesis. A DNA fragment containing the stop codon was generated using cosmid #9" as a template with the primers TCAGATGAACTTTATCGATAC, SEQ ID NO:65 and TCATGAGACGTCGTCGACTTACGCTTCAACAATACT, SEQ ID NO:66. The PCR product was digested with the restriction endonucleases *Cla*I and *Aat*II and was cloned into the cosmid 9" derivative digested with the same enzymes to yield plasmid 8P3. The *Sal*I fragment from 8P3 was cloned into *Sal*I digested pCGN7770 to yield pCGN8515.

PCGN8532, a binary plant transformation vector that contains a *Shewannella* ORF 3 under control of the napin promoter was digested with *Not*I, and a *Not*I fragment of pCGN8539 containing a napin *Vibrio* ORF 7 gene fusion was inserted to yield pCGN8552. Plasmid pCGN8556 (Figure 23), which contains *Shewannella* ORF 3, and *Vibrio* ORFs 7 and 9 under control of the napin promoter was constructed by cloning the *Sse*8357 fragment from pCGN8543 into *Sse*8387 digested pCGN8552.

The *Not*I digested napin/ORF 8 gene from plasmid pCGN8515 was cloned into a *Not*I digested plant binary transformation vector pCGN5139 to yield pCGN8548. The *Sse*8387 digested napin/ORF 6 gene from pCGN8554 was subsequently cloned into the *Sse*8387 site of pCGN8566. The resultant binary vector containing the napin/ORF 6 gene fusion and napin/ORF 8 gene fusion was designated pCGN8560 (Figure 22).

Example 5
Plant Transformation and PUFA Production

EPA production

The *Shewanella* constructs pCGN8535 and pCGN8537 can be transformed into the same or separate plants. If separate plants are used, the transgenic plants can be crossed resulting in heterozygous seed which contains both constructs.

pCGN8535 and pCGN8537 are separately transformed into *Brassica napus*. Plants are selected on media containing kanamycin and transformation by full length inserts of the constructs is verified by Southern analysis. Immature seeds also can be tested for protein expression of the enzyme encoded by ORFs 3, 6, 7, 8, or 9 using western analysis, in which case, the best expressing pCGNE8535 and pCGN8537 T_1 transformed plants are chosen and are grown out for further experimentation and crossing. Alternatively, the T_1 transformed plants showing insertion by Southern are crossed to one another producing T_2 seed which has both insertions. In this seed, half seeds may be analyzed directly from expression of EPA in the fatty acid fraction. Remaining half-seed of events with the best EPA production are grown out and developed through conventional breeding techniques to provide *Brassica* lines for production of EPA.

Plasmids pCGN7792 and pCGN7795 also are simultaneously introduced into *Brassica napus* host cells. A standard transformation protocol is used (*see* for example USPN 5,463,174 and USPN 5,750,871, however *Agrobacteria* containing both plasmids are mixed together and incubated with *Brassica* cotyledons during the cocultivation step. Many of the resultant plants are transformed with both plasmids.

DHA production

A plant is transformed for production of DHA by introducing pCGN8556 and pCGN8560, either into separate plants or simultaneously into the same plants as described for EPA production.

Alternatively, the *Shewanella* ORFs can be used in a concerted fashion with ORFs 6 and 8 of *Vibrio*, such as by transforming with a plant the constructs pCGN8560 and pCGN7795, allowing expression of the corresponding ORFs in a plant cell. This combination provides a PKS-like gene arrangement comprising ORFs 3, 7 and 9 of *Shewanella*, with an ORF 6 derived from *Vibrio* and also an OFR 8 derived from *Vibrio*. As described above, ORF 8 is the PKS-like gene which controls the identity of the final PUFA product. Thus, the resulting transformed plants produce DHA in plant oil.

Example 6

Transgenic plants containing the *Shewanella* PUFA genes

Brassica plants

Fifty-two plants cotransformed with plasmids pCGN8535 andpCGN8537 were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Forty-one plants contained plasmid pCGN8537, and thirty-five plants contained pCGN8535. 11 of the plants contained all five ORFs required for the synthesis of EPA. Several plants contained genes from both of the binary plasmids but appeared to be missing at least one of the ORFs. Analysis is currently being performed on approximately twenty additional plants.

Twenty-three plants transformed with pCGN8535 alone were analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Thirteen of these plants contained both *Shewanella* ORF 6 and *Shewanella* ORF 8. Six of the plants contained only one ORF.

Nineteen plants transformed with pCGN8537 were alone analyzed using PCR to determine if the *Shewanella* ORFs were present in the transgenic plants. Eighteen of the plants contained *Shewanella* ORF 3, *Shewanella* ORF 7, and *Shewanella* ORF 9. One plant contained *Shewanella* ORFs 3 and 7.

Arabidopsis

More than 40 transgenic Arabidopsis plants cotransformed with plasmids pCGN8535 and pCGN8537 are growing in our growth chambers. PCR analysis to determine which of the ORFs are present in the plants is currently underway.

Example 7

Evidence of A PKS System of PUFA Synthesis In *Schizochytrium*

The purpose of this experiment was to identify additional sources of PKS genes. Polyunsaturated long chain fatty acids were identified in *Schizochytrium* oil. Furthermore, production of polyunsaturated fatty acids was detected in a culture of *Schizochytrium*. A freshly diluted culture of *Schizochytrium* was incubated at 24°C in the presence of [^{14}C]-acetate (5uCi/mL) for 30 min with shaking (150 rpm). The cells were then collected by centrifugation, lyophilized and subjected to a transesterification protocol that involved heating to 90°C for 90 minutes in the presence of acidic (9% H_2SO_4) methanol with toluene (1 volume of toluene per two volumes of acidic methanol) as a second solvent. The resulting methylesters were extracted with an organic solvent (hexane) and separated by TLC (silica gel G, developed three times with hexane:diethyl ether (19:1)). Radioactivity on the TLC plate was detected using a scanner (AMBIS). Two prominent bands were detected on the TLC plate. These bands migrated on the TLC plate in positions expected for short chain (14 to 16 carbon), saturated methyl esters (the upper band) and with methylesters of polyunsaturated long chain (20 to 22 carbon) fatty acids (the lower band). These were also the major types of fatty acids detected by GC analysis of FAMEs of *Schizochytrium* oil.

In a parallel experiment thiolactomycin, a well known inhibitor of Type II fatty acid synthesis systems as well as several polyketide synthesis systems including EPA production by *E. coli* transformed with PKS genes derived from *Shewanella,* was added to the test tubes of varying concentrations (0, 1, 10 and 100 μg/ml) prior to addition of the *Schizochytrium* cell cultures and [^{14}C] acetate. Analysis of incorporation of [^{14}C] acetate, as described above, revealed that 100 ug/mL thiolactomycin completely blocked synthesis of polyunsaturated fatty acids, while partial inhibition of synthesis of polyunsaturated fatty acids was observed at 10 ug/mL thiolactomycin. Synthesis of the short chain saturated fatty acids was unaffected at all tested thiolactomycin concentrations. Thiolactomycin does not inhibit Type I fatty acid synthesis systems and is not toxic to mice, suggesting that it does not inhibit the elongation system leading to EPA or DHA formation. Furthermore, thiolactomycin did not inhibit the elongation system leading to PUFA synthesis in *Phaeodactylum tricornutum*. Therefore, although *Schizochytrium* is known to possess a Type I fatty acid synthesis system, the data suggested that the polyunsaturated fatty acids produced in this organism were derived from a system which was distinct from the Type I fatty acid synthesis system which produced short chain fatty acids, and from a system that was similar to the elongation/desaturation pathway found in mice and *Phaeodactylum*. The data are consistent with DHA formation being a result of a PKS pathway as found in *Vibrio marinus* and *Shewanella putrefaciens*.

Example 8
PKS Related Sequences From *Schizochytrium*

The purpose of this experiment was to identify sequences from *Schizochytrium* that encoded PKS genes. A cDNA library from *Schizochytrium* was constructed and approximately 8,000 random clones (ESTs) were sequenced. The protein sequence encoded by *Shewanella* EPA synthesis genes was compared to the predicted amino acid sequences of the *Schizochytrium* ESTs using a Smith/Waterman alignment algorithm. When the protein sequence of ORF6 (*Shewanella*) was compared with the amino acid sequences from *Schizochytrium* ESTs, 38 EST clones showed a significant degree of identity ($P<0.01$). When the protein sequence of ORF7 was compared by *Schizochytrium* ESTs, 4 EST clones showed significant identity ($P<0.01$) suggesting that the molecules were homologous. When the protein sequence of ORF8 and ORF9 were compared with the *Schizochytrium* ESTs, 7 and 14 clones respectively showed significant identity ($P<0.01$).

Example 9
Analysis of *Schizochytrium* cDNA Clones

Restriction enzyme analysis of the *Schizochytrium* EST clones was used to determine the longest clones, which were subsequently sequenced in their entirety. All of the EST sequences described in Example 8 were determined to be part of 5 cDNA clones.

Two of the cDNA clones were homologous to *Shewanella* ORF6. LIB3033-047-B5 was homologous to the C-terminus of ORF6. The sequence of LIB3033-047-B5 could be aligned with *Shewanella* ORF6 from amino acids 2093 onwards. The open reading frame of LIB3033-047-B5 extended all the way to the 5' end of the sequence, thus this clone was not likely to be full length. LIB3033-046-E6 shared homology to the ACP domain of ORF6. It contained 6 ACP repeats. This cDNA clone did not have a poly-A-tail, and therefore, it was likely to be a partial cDNA with additional regions of the cDNA found downstream of the sequence. The PCR primers GTGATGATCTTTCCCTGATGCACGCCAAGG (SEQ ID NO: 67) and AGCTCGAGACCGGCAACCCGCAGCGCCAGA (SEQ ID NO: 68) were used to amplify a fragment of approximately 500 nucleotides from *Schizochytrium* genomic DNA. Primer GTGATGATCTTTCCCTGATGCACGCCAAGG was derived from LIB3033-046-E6, and primer AGCTCGAGACCGGCAACCCGCAGCGCCAGA was derived from LIB3033-047-B5. Thus, LIB3033-046-E6 and LIB3033-047-B5 represented different portions of the same mRNA (see Figure 28) and could be assembled into a single partial cDNA sequence (see Figure 27A), SEQ ID NO: 69, that was predicted to encode a protein with the sequence in Figure 29A (SEQ ID NO: 70). The open reading frame extended all the way to the 5' end of the sequence, thus this partial cDNA was not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by clones LIB3033-046-E6 and LIB3033-047-B5. It may contain condensing enzyme related domains similar to those found near the N-terminus of *Shewanella* ORF6.

One of the cDNA clones, LIB3033-046-D2, was homologous to *Shewanella* ORF9 at its 3' end. This clone was homologous to the chain length factor region of *Shewanella* ORF8 at its 5' end. This clone was also homologous to the entire open reading frame of the *Anabaena* HglC ORF. The *Anabaena* HglC ORF is homologous to the chain length factor region of *Shewanella* ORF8 and *Shewanella* ORF7. Thus this cDNA (Figure 27B), SEQ ID NO: 71, was homologous to part of *Shewanella* ORF8, *Shewanella* ORF7 and *Shewanella* ORF9 (see Figure 28). The amino acid sequence (Figure 29B), SEQ ID NO: 72, encoded by the open reading frame of LIB3033-046-D2 extended all the way to the 5' end of the sequence; thus this clone was not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by LIB3033-046-E6. It may contain condensing enzyme related domains similar to those found near the N-terminus of *Shewanella* ORF8.

Two additional cDNA clones were homologous to *Shewanella* ORF8. LIB81-015-D5 was homologous to the C-terminus of ORF8. The 5' sequence of LIB81-015-D5 could be

aligned with *Shewanella* ORF8 from amino acids 1900 onwards. The 3' end of LIB81-015-D5 could be aligned with *Shewanella* ORF9 (see Figure 28). The amino acid sequence (Figure 29C), SEQ ID NO: 73, encoded by the open reading frame of LIB81-015-D5 extended all the way to the 5' end of the sequence; thus this clone was not likely to be full length. LIB81-042-B9 was homologous to amino acids 1150 to 1850 of *Shewanella* ORF8. LIB81-042-B9 did not have a poly-A-tail, and therefore, it was likely to be a partial cDNA with additional regions of the cDNA found downstream of the sequence. The PCR primers TACCGCGGCAAGACTATCCGCAACGTCACC (SEQ ID NO: 74) and GCCGTCGTGGGCGTCCACGGACACGATGTG (SEQ ID NO: 75) were used to amplify a fragment of approximately 500 nucleotides from *Schizochytrium* genomic DNA. Primer TACCGCGGCAAGACTATCCGCAACGTCACC was derived from LIB81-042-B9, and primer GCCGTCGTGGGCGTCCACGGACACGATGTG was derived from LIB81-015-D5. Thus, LIB81-042-and LIB81-015-D5 represented different portions of the same mRNA and were assembled into a single partial cDNA sequence (see Figure 27C), SEQ ID NO: 76. The open reading frame of LIB81-042-B9 also extended all the way to the 5' end of the sequence, thus this clone was also not likely to be full length. Analysis of additional cDNA or genomic clones will allow the determination of the full extent of the mRNA represented by LIB81-042-B9.

By the present invention PKS-like genes from various organisms can now be used to transform plant cells and modify the fatty acid compositions of plant cell membranes or plant seed oils through the biosynthesis of PUFAs in the transformed plant cells. Due to the nature of the PKS-like systems, fatty acid end-products produced in the plant cells can be selected or designed to contain a number of specific chemical structures. For example, the fatty acids can comprise the following variants: Variations in the numbers of keto or hydroxyl groups at various positions along the carbon chain; variations in the numbers and types (*cis* or *trans*) of double bonds; variations in the numbers and types of branches off of the linear carbon chain (methyl, ethyl, or longer branched moieties); and variations in saturated carbons. In addition, the particular length of the end-product fatty acid can be controlled by the particular PKS-like genes utilized.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

<u>What is claimed is:</u>

1. An isolated nucleic acid comprising:

a *Vibrio marinus* nucleotide sequence selected from the group consisting of ORF 6 (SEQ ID NO:77), ORF 7 (SEQ ID NO:78), ORF 8 (SEQ ID NO:79), and ORF 9 (SEQ ID NO:80), as shown in Figure 6.

2. An isolated nucleic acid comprising:

a nucleotide sequence which encodes a polypeptide of a polyketide-like synthesis system, wherein said system produces a docosahexenoic acid when expressed in a host cell.

3. The isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is derived from a marine bacterium.

4. An isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is derived from *Schizochytrium*.

5. The isolated nucleic acid according to Claim 2, wherein said nucleotide sequence is a *Vibrio marinus* ORF 8 (SEQ ID NO:79), as shown in Figure 6.

6. An isolated nucleic acid comprising a *Schizochytrium* nucleotide sequence comprising a sequence shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71 and 76.

7. An isolated nucleic acid comprising:

a nucleotide sequence which is substantially identical to a sequence of at least 50 nucleotides of a *Vibrio marinus* nucleotide sequence selected from the group consisting of ORF 6 (SEQ ID NO:77), ORF 7 (SEQ ID NO:78), ORF 8 (SEQ ID NO:79), and ORF 9 (SEQ ID NO:80), as shown in Figure 6.

8. A recombinant microbial cell comprising at least one copy of an isolated nucleic acid according to Claim 6.

9. The recombinant microbial cell according to Claim 8, wherein said cell comprises each element of a polyketide-like synthesis system required to produce a long chain polyunsaturated fatty acid.

10. The recombinant microbial cell according to Claim 9, wherein said cell is a eukaryotic cell.

11. The recombinant microbial cell according to Claim 10, wherein said eukaryotic cell is a fungal cell, an algae cell or an animal cell.

12. The recombinant microbial cell according to Claim 11, wherein said fungal cell is a yeast cell and said algae cell is a marine algae cell.

13. The recombinant microbial cell according to Claim 8, wherein said cell is a prokaryotic cell.

14. The recombinant microbial cell according to Claim 13, wherein said cell is a bacterial cell or a cyanobacterial cell.

15. A recombinant cell according to Claim 14, wherein said bacterial cell is a *lactobacillus* cell.

16. The microbial cell according to Claim 8, wherein said recombinant microbial cell is enriched for 22:6 fatty acids as compared to a non-recombinant microbial cell which is devoid of said isolated nucleic acid.

17. A method for production of docosahexenoic acid in a microbial cell culture, said method comprising:

growing a microbial cell culture having a plurality of microbial cells, wherein said microbial cells or ancestors of said microbial cells were transformed with a vector comprising one or more nucleic acids having a nucleotide sequence which encodes a polypeptide of a polyketide synthesizing system, wherein said one or more nucleic acids are operably linked to a promoter, under conditions whereby said one or more nucleic acids are expressed and docosahexenoic acid is produced in said microbial cell culture.

18. A method for production of a long chain polyunsaturated fatty acid in a plant cell, said method comprising:

growing a plant having a plurality of plant cells, wherein said plant cells or ancestors of said plant cells were transformed with a vector comprising one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic

acids are operably linked to a promoter functional in a plant cell, under conditions whereby said polypeptides are expressed and a long chain polyunsaturated fatty acid is produced in said plant cells.

19. The method according to Claim 17 or Claim 18 wherein said nucleotide sequence is shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71 and 76.

20. The method according to Claim 18, wherein said long chain polyunsaturated fatty acid produced in said plant cells is a 20:5 and 22:6 fatty acid.

21. The method according to Claim 17, wherein said nucleotide sequence is selected from the group consisting of *Vibrio marinus* ORF 6 (SEQ ID NO:77), ORF 7 (SEQ ID NO:78), ORF 8 (SEQ ID NO:79), and ORF 9 (SEQ ID NO:80), as shown in Figure 6 and *Shewanella putrefaciens* ORF 6 (SEQ ID NO:83), ORF 7 (SEQ ID NO:84), ORF 8 (SEQ ID NO:85), ORF 9 (SEQ ID NO:86), and ORF 3, which is complementary to SEQ ID NO:4, as shown in Figure 4.

22. The method according to Claim 18, wherein said nucleic acid constructs are derived from two or more polyketide synthesizing systems.

23. The method according to Claim 18, wherein said long chain polyunsaturated fatty acid is eicosapentenoic acid.

24. The method according to Claim 18, wherein said long chain polyunsaturated fatty acid is docosahexenoic acid.

25. A recombinant plant cell comprising:

one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic acids are operably linked to a promoter functional in said plant cell.

26. The recombinant plant cell according to Claim 25, wherein said nucleotide sequence is shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71 and 76.

27. The recombinant plant cell according to Claim 26, wherein said recombinant plant cell is a recombinant seed cell.

28. The recombinant plant cell according to Claim 27, wherein said recombinant seed cell is a recombinant embryo cell.

29. The recombinant plant cell according to Claim 26, wherein said recombinant plant cell is from a plant selected from the group consisting of *Brassica*, soybean, safflower, and sunflower.

30. A plant oil produced by a recombinant plant cell according to Claim 26.

31. The plant oil according to Claim 30, wherein said plant oil comprises eicosapentenoic acid.

32. The plant oil according to Claim 30, wherein said plant oil comprises docosahexenoic acid.

33. The plant oil according to Claim 30, wherein said plant oil is encapsulated.

34. A dietary supplement comprising a plant oil according to Claim 30.

35. A recombinant *E. coli* cell comprising:

one or more nucleic acids having a nucleotide sequence which encodes one or more polypeptides of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid, wherein each of said nucleic acids are operably linked to a promoter function in said *E. coli* cell.

36. The recombinant *E. coli* cell according to Claim 35, wherein said long chain polyunsaturated fatty acid is docosahexenoic acid.

37. The recombinant *E. coli* cell according to Claim 35, wherein said nucleotide sequence is shown in a SEQ ID NO selected from the group consisting of SEQ ID NOS: 69, 71 and 76.

38. A plant oil produced by a recombinant plant cell wherein said plant oil comprises a long chain polyunsaturated fatty acid exogenous to said plant oil, wherein said plant cell is produced according to a method comprising:

transforming said plant cell or an ancestor of said plant cell with a vector comprising one or more polypeptide of a polyketide synthesizing system which produces a long chain polyunsaturated fatty acid wherein each of said nucleic acids are operably linked to a promoter functional in said plant cell.

39. A plant oil according to Claim 38, wherein said long chain polyunsaturated fatty acid is eicosapentenoic acid.

40. A plant oil according to Claim 38, wherein said long chain polyunsaturated fatty acid is docosahexenoic acid.

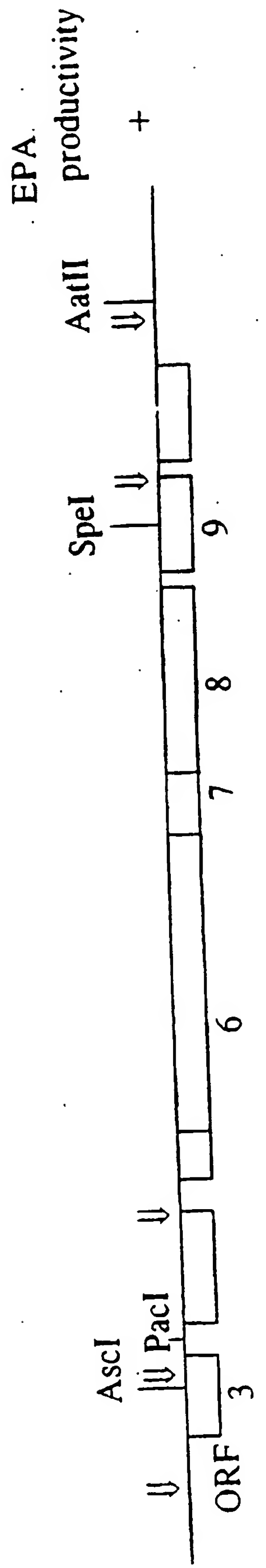

FIG. 1A

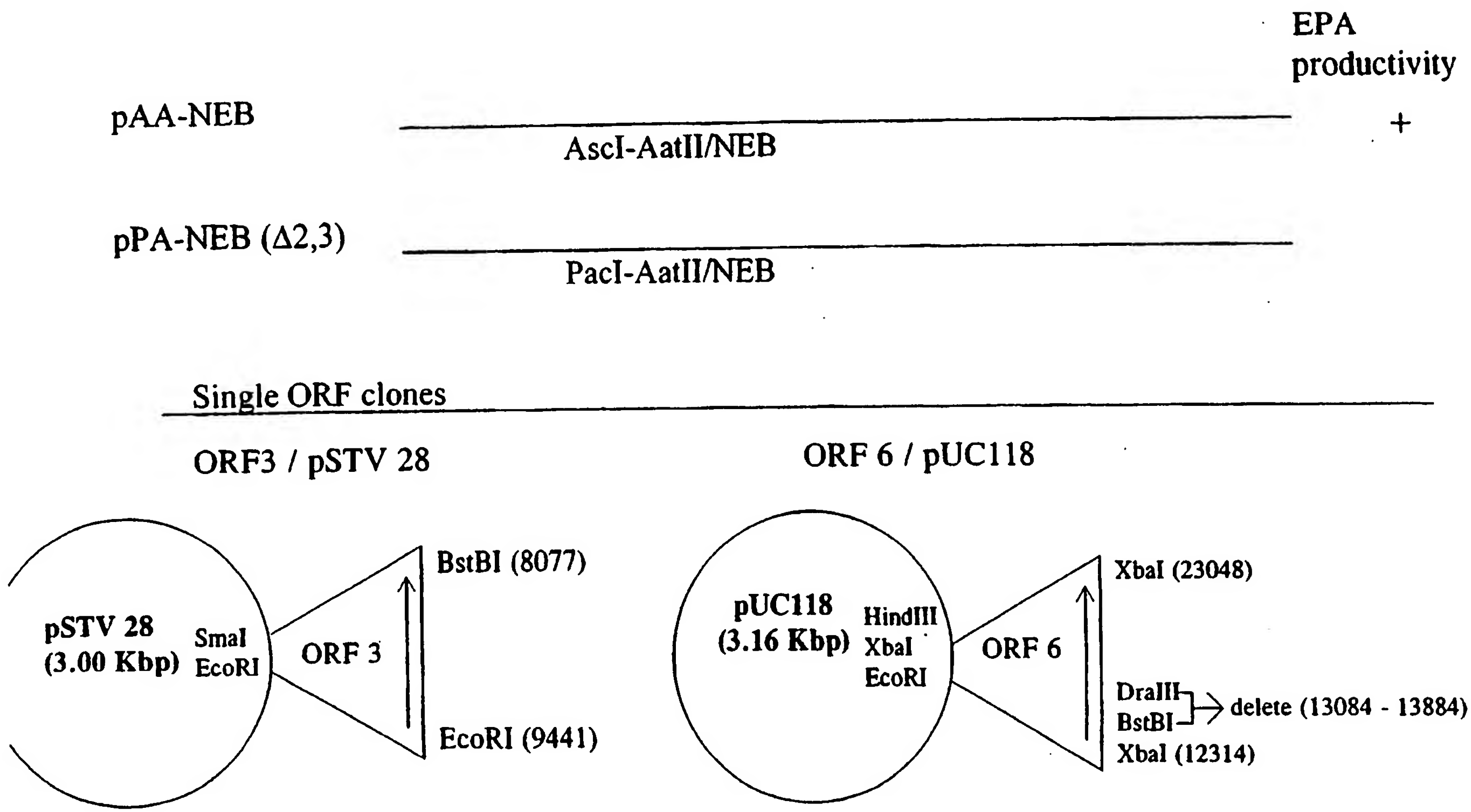
EPA
productivity
pAA-NEB
AscI-AatII/NEB
+
pPA-NEB (Δ2,3)
PacI-AatII/NEB
Single ORF clones
ORF3 / pSTV 28
ORF 6 / pUC118
pSTV 28
(3.00 Kbp)
SmaI
EcoRI
ORF 3
BstBI (8077)
EcoRI (9441)
pUC118
(3.16 Kbp)
HindIII
XbaI
EcoRI
ORF 6
XbaI (23048)
DraIII
BstBI
delete (13084 - 13884)
XbaI (12314)

FIG. 1B

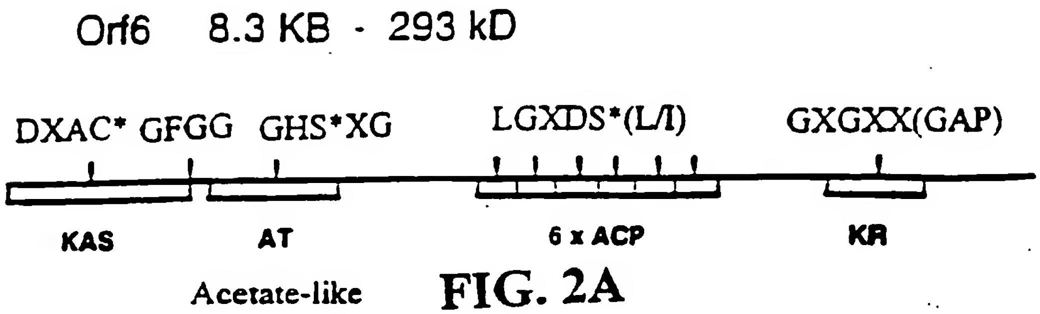

FIG. 2A

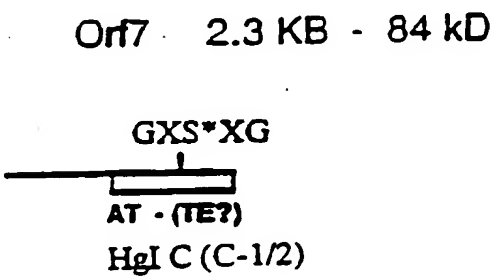

FIG. 2B

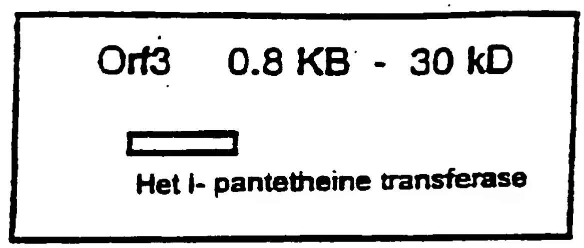

FIG. 2E

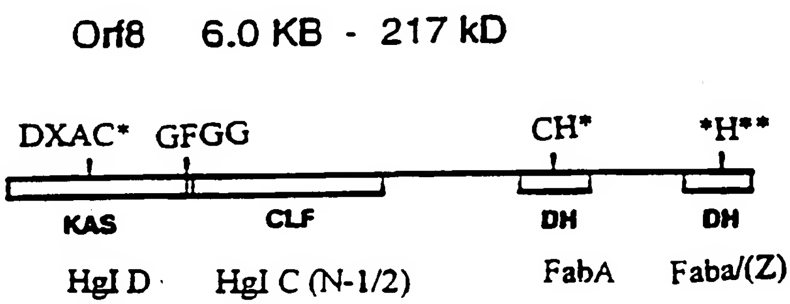

FIG. 2C

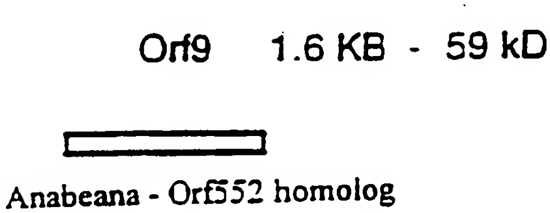

FIG. 2D

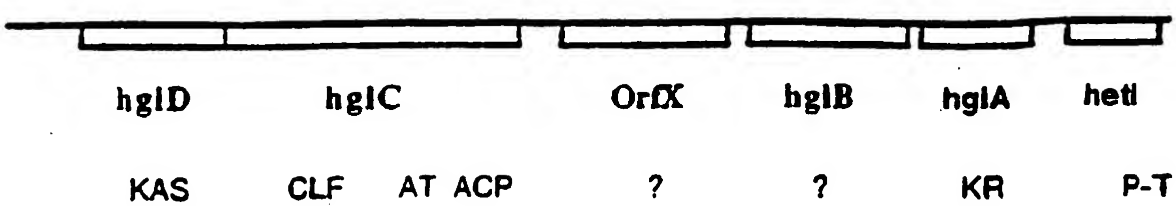

FIG. 2F

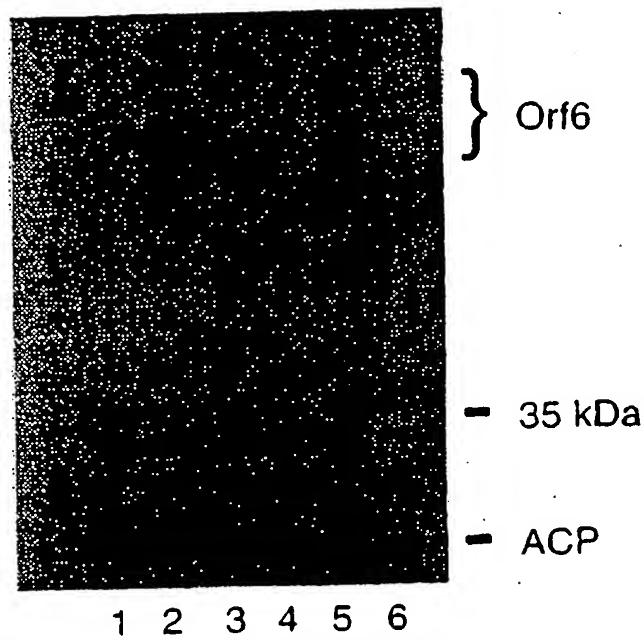

FIG. 3

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GATCTCTTAC AAAGAAACTA TCTCAATGTG AATTTAACCT TAATTCCGTT TAATTACGGC 60
CTGATAGAGC ATCACCCAAT CAGCCATAAA ACTGTAAAGT GGGTACTCAA AGGTGGCTGG 120
GCGATTCTTC TCAAATACAA AGTGCCCAAC CCAAGCAAAT CCATATCCGA TAACAGGTAA 180
AAGTAGCAAT AAACCCCAGC GCTGAGTTAG TAATACATAA GCGAATAATA GGATCACTAA 240
ACTACTGCCG AAATAGTGTA ATATTCGACA GTTTCTATGC TGATGTTGAG ATAAATAAAA 300
AGGGTAAAAT TCAGCAAAAG AACGATAGCG CTTACTCATT ACTCACACCT CGGTAAAAAA 360
GCAACTCGCC ATTAACTTGG CCAATCGTCA GTTGTTCTAT CGTCTCAAAG TTATGCCGAC 420
TAAATAACTC TATATGTGCA TTATGATTAG CAAAAACTCC GATACCATCA AGATGAAGTT 480
GTTCATCACA CCAACTCAAA ACTGCGTCGA TAAGCTTACT GCCATAGCCC TTGCCTTGCT 540
CCACATTTGC GATAGCAATA AACTGTAAAA TGCCACATTG GCCACTTGGT AAGCTCTCTA 600
TAATCTGATT TTCTTTGTTA ATAAGTGCCT GAGTTGAATA CCAACCAGTA CTTAACAACA 660
TCTTTAAACG CCAATGCCAA AAACGCGCTT CACCTAAGGG AACCTGCTGA GTCACTATGC 720
AGGCTACGCC TATCAATCTA TCCCCAACGA ACATACCAAT AAGTGCTTGC TCCTGTTGCC 780
AGAGCTCATT GAGTTCTTCT CGAATAGCCC CGCGAAGCTT TTGCTCATAC TGCGCTTGAT 840
CACCACTAAA AAGTGTTTCG ATAAAAAAGG GATCATCATG ATAGGCGTTA TAGAGAATAG 900
AGGCTGCTAT GCGTAAATCT TCTGCCGTGA GATAAACTGC ACGACACTCT TCCATGGCTT 960
GATCTTCCAT TGTTATTGTC CTTGACCTTG ATCACACAAC ACCAATGTAA CAAGACTGTA 1020
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FIG. 4A-1

TAGAAGTGCA ATTAATAATC AATTCGTGCA TTAAGCAGGT CAGCATTTCT TTGCTAAACA 1080
AGCTTTATTG GCTTTGACAA AACTTTGCCT AGACTTTAAC GATAGAAATC ATAATGAAAG 1140
AGAAAAGCTA CAACCTAGAG GGGAATAATC AAACAACTGC TAAGATCTAG ATAATGTAAT 1200
AAACACCGAG TTTATCGACC ATACTTAGAT AGAGTCATAG CAACGAGAAT AGTTATGGAT 1260
ACAACGCCGC AAGATCTATC ACACCTGTTT TTACAGCTAG GATTAGCAAA TGATCAACCC 1320
GCAATTGAAC AGTTTATCAA TGACCATCAA TTAGCGGACA ATATATTGCT ACATCAAGCA 1380
AGCTTTTGGA GCCCATCGCA AAAGCACTTC TTAATTGAGT CATTTAATGA AGATGCCCAG 1440
TGGACCGAAG TCATCGACCA CTTAGACACC TTATTAAGAA AAAACTAACC ATTACAACAG 1500
CAACTTTAAA TTTTGCCGTA AGCCATCTCC CCCCACCCCA CAACAGCGTT GTTGCTTATG 1560
ACCACTGGAG TACATTCGTC TTTAGTCGTT TTACCATCAC CATGGGTACG TTGAGTGCGA 1620
TAAAAAAGCA CATAAACTTC TTTATCGGCC TGAATATAGG CTTCGTTAAA ATCAGCTGTT 1680
CCCATTAAAG TAACCACTTG CTCTTTACTC ATGCCTAGAG ATATCTTTGT CAAATTGTCA 1740
CGGTTTTTAT CTTGAGTTTT CTCCCAAGCA CCGTGATTAT CCCAGTCAGA TTCCCCATCA 1800
CCAACATTGA CCACACAGCC CGTTAGCCCT AAGCTTGCAA TCCCAAAACA TGCTAAACCT 1860
AATAATTTAT TTTTCATTTT AACTTCCTGT TATGACATTA TTTTTGCTTA GAAGAAAAGC 1920
AACTTACATG CCAAAACACA AGCTGTTGTT TTAAATGACT TTATTTATTA TTAGCCTTTT 1980
AGGATATGCC TAGAGCAATA ATAATTACCA ATGTTTAAGG AATTTGACTA ACTATGAGTC 2040

FIG. 4A-2

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CGATTGAGCA AGTGCTAACA GCTGCTAAAA AAATCAATGA ACAAGGTAGA GAACCAACAT 2100
TAGCATTGAT TAAAACCAAA CTTGGTAATA GCATCCCAAT GCGCGAGTTA ATCCAAGGTT 2160
TGCAACAGTT TAAGTCTATG AGTGCAGAAG AAAGACAAGC AATACCTAGC AGCTTAGCAA 2220
CAGCAAAAGA AACTCAATAT GGTCAATCAA GCTTATCTCA ATCTGAACAA GCTGATAGGA 2280
TCCTCCAGCT AGAAAACGCC CTCAATGAAT TAAGAAACGA ATTTAATGGG CTAAAAAGTC 2340
AATTTGATAA CTTACAACAA AACCTGATGA ATAAAGAGCC TGACACCAAA TGCATGTAAT 2400
TGAACTACGA TTTGAATGTT TTGATAACAC CACGATTACT GCAGCAGAAA AAGCCATTAA 2460
TGGTTTGCTT GAAGCTTATC GAGCCAATGG CCAGGTTCTA GGTCGTGAAT TTGCCGTTGC 2520
ATTTAACGAT GGTGAGTTTA AAGCACGCAT GTTAACCCCA GAAAAAAGCA GCTTATCTAA 2580
ACGCTTTAAT AGTCCTTGGG TAAATAGTGC ACTCGAAGAG CTAACCGAAG CCAAATTGCT 2640
TGCGCCACGT GAAAAGTATA TTGGCCAAGA TATTAATTCT GAAGCATCTA GCCAAGACAC 2700
ACCAAGTTGG CAGCTACTTT ACACAAGTTA TGTGCACATG TGCTCACCAC TAAGAAATGG 2760
CGACACCTTG CAGCCTATTC CACTGTATCA AATTCCAGCA ACTGCCAACG GCGATCATAA 2820
ACGAATGATC CGTTGGCAAA CAGAATGGCA AGCTTGTGAT GAATTGCAAA TGGCCGCAGC 2880
TACTAAAGCT GAATTTGCCG CACTTGAAGA GCTAACCAGT CATCAGAGTG ATCTATTTAG 2940
GCGTGGTTGG GACTTACGTG GCAGAGTCGA ATACTTGACG AAAATTCCGA CCTATTACTA 3000
TTTATACCGT GTTGGCGGTG AAAGCTTAGC AGTAGAAAAG CAGCGCTCTT GTCCTAAGTG 3060
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FIG. 4A-3

TGGCAGTCAA GAATGGCTGC TCGATAAACC ATTATTGGAT ATGTTCCATT TTCGCTGTGA 3120
CACCTGCCGC ATCGTATCTA ATATCTCTTG GGACCATTTA TAACTCTTCC GAGTCTTATC 3180
ACACTAGAGT TTAGTCAGCA TAAAAATGGC GCTTATATTT CAATTAAAAG AAATATAAGC 3240
GCCATTTTCA TCGATACTAT ATATCAGCAG ACTATTTTCC GCGTAAATTA GCCCACATTA 3300
ATTTCATTCT TTGCCAGATC CCTGGATGAT CTAGTTGTGG CATCGACTCT TCAATAGGTT 3360
TAACCGCAGG TGTAACCCTT GGAGTCAATT CGTTTATAAA CTCGTTTAAA CTGTCACTTA 3420
ATTTAACGCT TTGTACTTCA CCTGGAATTT CAATCCATAC GCTGCCATCA CTATTATTAA 3480
CCGTCAACAT TTTATCTTCA TCATCAAGAA TACCAATAAA CCAAGTCGGC TCTTGCTTAA 3540
GCTTTCTCTT CATCATTAAA TGACCAATGA TGTTTTGTTG TAAGTATTCA AAATCAGTTT 3600
GATCCCACAC TTGGATTAGC TCACCTTGGC CCCATTGTGA GTCAAAAAAT AGCGGTGCAG 3660
AAAAATGACT GCCAAAAAAT GGATTAATTT CTGCAGATAA TGTCATTTCA AGTGCTGTTT 3720
CAACATTAGC AAATTCACCA GGTTGTTGAC GTACAACCGA TTGCCAAAAC ACTGCGCCAT 3780
CGGAGCCCGC TTCGGCGACA ACACACTCAG ACTTTTGTCC TTGCGCATAA TATCTTGGCT 3840
GTTCACCAAG CTTATCCATG TAGGCTTGTT GATATTTAGA TAAAAAAAGA TCTAAAGCAG 3900
GTAAAGAAGA CACTTAAGCC AGTTCCAAAA TCAGTTATAA TAGGGGTCTA TTTTGACATG 3960
GAAACCGTAT TGATGACACA ACATCATGAT CCCTACAGTA ACGCCCCCGA ACTTTCTGAA 4020
TTAACTTTAG GAAAGTCGAC CGGTTATCAA GAGCAGTATG ATGCATCTTT ACTACAAGCG 4080

FIG. 4A-4

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TGCCGCGTAA ATTAAACCGT GATGCTATCG GTCTAACCAA TGAGCTACCT TTTCATGGCT 4140
GTGATATTTG GACTGGCTAC GAACTGTCTT GGCTAAATGC TAAAGGCAAG CCAATGATTG 4200
CTATTGCAGA CTTTAACCTA AGTTTTGATA GTAAAAATCT GATCGAGTCT AAGTCGTTTA 4260
AGCTGTATTT AAACAGCTAT AACCAAACAC GATTTGATAG CGTTCAAGCG GTTCAAGAAC 4320
GTTTAACTGA AGACTTAAGC GCCTGTGCCC AAGGCACAGT TACGGTAAAA GTGATTGAAC 4380
CTAAGCAATT TAACCACCTG AGAGTGGTTG ATATGCCAGG TACCTGCATT GACGATTTAG 4440
ATATTGAAGT TGATGACTAT AGCTTTAACT CTGACTATCT CACCGACAGT GTTGATGACA 4500
AAGTCATGGT TGCTGAAACG CTAACGTCAA ACTTATTGAA ATCAAACTGC CTAATCACTT 4560
CTCAGCCTGA CTGGGGTACA GTGATGATCC GTTATCAAGG GCCTAAGATA GACCGTGAAA 4620
AGCTACTTAG ATATCTGATT TCATTTAGAC AGCACAATGA ATTTCATGAG CAGTGTGTTG 4680
AGCGTATATT TGTTGATTTA AAGCACTATT GCCAATGTGC CAAACTTACT GTCTATGCAC 4740
GTTATACCCG CCGTGGTGGT TTAGATATCA ACCCATATCG TAGCGACTTT GAAAACCCTG 4800
CAGAAAATCA GCGCCTAGCG AGACAGTAAT TGATTGCAGT ACCTACAAAA AACAATGCCT 4860
ATAAGCCAAG CTTATGGGCA TTTTTATATT ATCAACTTGT CATCAAACCT CAGCCGCCAA 4920
GCCTTTTAGT TTTATCGCTA AATTAAGCCG CTCTCTCAGC CAAATATTTG CAGGATTTTG 4980
CTGTAATTTA TGGCTCCACA CCATGAAATA CTCTATCGGC TCTACCGCAA AAGGTAAGTC 5040
AAATACCTGT AAGCCAAACA GCTTGGCATA TTCGTCAGTG TGGGCTTTTG ACGCGATAGC 5100
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FIG. 4A-5

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TAACGCATCA CTTTTTGAGG CAACCGACAT CATACTTAAT ATTGATGATT GCTCGCTGTG 5160
CATTTGCCTT GCCGGTAACA CCTGTTTAGT CAGCAAGTCG GCAACACTTA AATTGTAGCG 5220
GCGCATCTTA AAAATAATAT GCTTTTCATT AAAGTATTGC TCTTGCGTCA ACCCACCTTG 5280
GATCCTTGGG TGAGCATTTC GTGCCACACA AACTAATTTA TCCTGCATTA CTTTTTGACT 5340
CTTAAATGCC GCAGATTCTG GCAGCCAAAT ATCTAAGGCT AAATCCACCT TTTCTAGTTG 5400
TAGGTCCATC TGCAACTCTT CTTCAATGAG CGGCGGCTCA CGAAATACAA TATTAATTGC 5460
AGTGCCCTGT AACACTTGCT CAATTTGATC TTGCAAGAGT TGTATTGCCG ACTCGCTGGC 5520
ATACACATAA AAAGTTCGCT CACTTGAAGT GGGGTCAAAT GCTTCAAAGC TAGTCGCAAC 5580
TTGCTCAATT GTTGACATAG CGCCCGCGAG CTGTTGATAA AGCGTCATCG CACTTGCGGT 5640
AGGTTTAACT CCCCTACCCA CTCGAGTAAA CAACTCTTCT CCAACAATAC TTTTTAGCCT 5700
CGAAATCGCA TTACTAACCG ACGACTGAGT CAAATCCAGC TCTTCTGCCG CCCGGCTAAA 5760
AGATGAGGTG CGATACACCG CAGTAAAAAC GCGAAATAAA TTAAGATCAA AAGCTTTTTG 5820
CTGCGACATA AATCAGCTAT CTCCTTATCC TTATCCTTAT CCTTATAAAA AGTTAGCTCC 5880
AGAGCACTCT AGCTCAAAAA CAACTCAGCG TATTAAGCCA ATATTTTGGG AACTCAATTA 5940
ATATTCATAA TAAAAGTATT CATAATATAA ATACCAAGTC ATAATTTAGC CCTAATTATT 6000
AATCAATTCA AGTTACCTAT ACTGGCCTCA ATTAAGCAAA TGTCTCATCA GTCTCCCTGC 6060
AACTAAATGC AATATTGAGA CATAAAGCTT TGAACTGATT CAATCTTACG AGGGTAACTT 6120
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FIG. 4A-6

ATGAAACAGA CTCTAATGGC TATCTCAATC ATGTCGCTTT TTTCATTCAA TGCGCTAGCA 6180
GCGCAACATG AACATGACCA CATCACTGTT GATTACGAAG GGAAAGCCGC AACAGAACAC 6240
ACCATAGCTC ACAACCAAGC TGTAGCTAAA ACACTTAACT TTGCCGACAC GCGTGCATTT 6300
GAGCAATCGT CTAAAAATCT AGTCGCCAAG TTTGATAAAG CAACTGCCGA TATATTACGT 6360
GCCGAATTTG CTTTTATTAG CGATGAAATC CCTGACTCGG TTAACCCGTC TCTCTACCGT 6420
CAGGCTCAGC TTAATATGGT GCCTAATGGT CTGTATAAAG TGAGCGATGG CATTTACCAG 6480
GTCCGCGGTA CCGACTTATC TAACCTTACA CTTATCCGCA GTGATAACGG TTGGATAGCA 6540
TACGATGTTT TGTTAACCAA AGAAGCAGCA AAAGCCTCAC TACAATTTGC GTTAAAGAAT 6600
CTACCTAAAG ATGGCGATTT ACCCGTTGTT GCGATGATTT ACTCCCATAG CCATGCGGAC 6660
CACTTTGGCG GAGCTCGCGG TGTTCAAGAG ATGTTCCCTG ATGTCAAAGT CTACGGCTCA 6720
GATAACATCA CTAAAGAAAT TGTCGATGAG AACGTACTTG CCGGTAACGC CATGAGCCGC 6780
CGCGCAGCTT ATCAATACGG CGCAACACTG GGCAAACATG ACCACGGTAT TGTTGATGCT 6840
GCGCTAGGTA AAGGTCTATC AAAAGGTGAA ATCACTTACG TCGCCCCAGA CTACACCTTA 6900
AACAGTGAAG GCAAATGGGA AACGCTGACG ATTGATGGTC TAGAGATGGT GTTTATGGAT 7960
GCCTCGGGCA CCGAAGCTGA GTCAGAAATG ATCACTTATA TTCCCTCTAA AAAAGCGCTC 7020
TGGACGGCGG AGCTTACCTA TCAAGGTATG CACAACATTT ATACGCTGCG CGGCGCTAAA 7080
GTACGTGATG CGCTCAAGTG GTCAAAAGAT ATCAACGAAA TGATCAATGC CTTTGGTCAA 7140

FIG. 4A-7

GATGTCGAAG TGCTGTTTGC CTCGCACTCT GCGCCAGTGT GGGGTAACCA AGCGATCAAC 7200
GATTTCTTAC GCCTACAGCG TGATAACTAC GGCCTAGTGC ACAATCAAAC CTTGAGACTT 7260
GCCAACGATG GTGTCGGTAT ACAAGATATT GGCGATGCGA TTCAAGACAC GATTCCAGAG 7320
TCTATCTACA AGACGTGGCA TACCAATGGT TACCACGGCA CTTATAGCCA TAACGCTAAA 7380
GCGGTTTATA ACAAGTATCT AGGCTACTTC GATATGAACC CAGCCAACCT TAATCCGCTG 7440
CCAACCAAGC AAGAATCTGC CAAGTTTGTC GAATACATGG GCGGCGCAGA TGCCGCAATT 7500
AAGCGCGCTA AAGATGATTA CGCTCAAGGT GAATACCGCT TTGTTGCAAC GGCATTAAAT 7560
AAGGTGGTGA TGGCCGAGCC AGAAAATGAC TCCGCTCGTC AATTGCTAGC CGATACCTAT 7620
GAGCAACTTG GTTATCAAGC AGAAGGGGCT GGCTGGAGAA ACATTTACTT AACTGGCGCA 7680
CAAGAGCTAC GAGTAGGTAT TCAAGCTGGC GCGCCTAAAA CCGCATCGGC AGATGTCATC 7740
AGTGAAATGG ACATGCCGAC TCTATTTGAC TTCCTCGCGG TGAAGATTGA TAGTCAACAG 7800
GCGGCTAAGC ACGGCTTAGT TAAGATGAAT GTTATCACCC CTGATACTAA AGATATTCTC 7860
TATATTGAGC TAAGCAACGG TAACTTAAGC AACGCAGTGG TCGACAAAGA GCAAGCAGCT 7920
GACGCAAACC TTATGGTTAA TAAAGCTGAC GTTAACCGCA TCTTACTTGG CCAAGTAACC 7980
CTAAAAGCGT TATTAGCCAG CGGCGATGCC AAGCTCACTG GTGATAAAAC GGCATTTAGT 8040
AAAATAGCCG ATAGCATGGT CGAGTTTACA CCTGACTTCG AAATCGTACC AACGCCTGTT 8100
AAATGAGGCA TTAATCTCAA CAAGTGCAAG CTAGACATAA AAATGGGGCG ATTAGACGCC 8160

FIG. 4A-8

CCATTTTTTA TGCAATTTTG AACTAGCTAG TCTTAGCTGA AGCTCGAACA ACAGCTTTAA 8220
AATTCACTTC TTCTGCTGCA ATACTTATTT GCTGACACTG ACCAATACTC AGTGCAAAAC 8280
GATAACTATC ATCAAGATGG CCCAGTAAAC AATGCCAATT ATCAGCAGCG TTCATTTGCT 8340
GTTCTTTAGC CTCAATCAAA CCTAAACCAG ACTTTTGTGG CTCAGCGTTA GGCTTATTAG 8400
AACTCGACTC TAGTAAAGCA AGACCAATAT CTTGTTTTAA CAAAACCTGT CGCTGATTAA 8460
GTTGATGCTC AACCTTGTGA TCCGCAATAG CATCGGAAAT ATCAACACAA TGGCTCAAGC 8520
TTTTAGGTGC ATTAACTCCA AGAAAAGTTT CGCTCAGTGC AGAGAAGTCA AACGCAAAAG 8580
ATTTTAGCGA TAATGCCAGC CCAAGTCCTT TCGCTTTAAT GTAAGACTCC TTGAGCGCCC 8640
ACAAATCAAA AAAGCGGTCT CGCTGCAAGG CCTCTGGTAA CGCTAACAAG GCTCGCTTTT 8700
CTGATTCAGA GAAATAATGA CTAAGAATAG AGTGGATATT GGTGCTGTTA CGGCAACGCT 8760
CAATGTCGAC GCCAAACTCA ATACTAGCAG AGTCAGTTTC CTCCTTGCTT GCCTGACTGG 8820
CGCCTTTATT ATCAGCAGTG CAAATGCCTA CTAATAGCCA ATCTCCACTA TGACTCACAT 8880
TAAAGTGGAC CCCGGTTTGA GCAAATTGCG CATCACTCAA TCTAGGCTTA CCTTTGTCGC 8940
CATATTCAAA GCGCCATTCA TTGGGGCGTA TTTCACTATG TTGTGACAAT AAAGCGCGCA 9000
AATAGCCTCT TACCATTAAA CCTTGAGTTT TAGCTTCTTG TTTAATGTAG CGATTAACCT 9060
TAATTAACTC ATCTTCAGGC AGCCATGACT TAACCAACTC TGTAGTCTGG TTATCGCACT 9120
CTTGTATTGT TAACGGACAG AAGTATAAGG AAATCAATCG AGAAGTTAGC AATTTTTCAG 9180

FIG. 4A-9

GACACTCTTT AAAGCAACAA ACATAACCCC TATTTTTACC AATTTAAGAT CAAAACTAAA 9240
GCCAAAACTA ATTGAGAATA GTGTCAAACT AGCTTTAAAG GAAAAAAATA TAAAAAGAAC 9300
ATTATACTTG TATAAATTAT TTTACACACC AAAGCCATGA TCTTCACAAA ATTAGCTCCC 9360
TCTCCCTAAA ACAAGATTGA ATAAAAAAAT AAACCTTAAC TTTCATATAG ATAAAACAAA 9420
CCAATGGGAT AAAGTATATT GAATTCATTT TTAAGGAAAA ATTCAAATTG AATTCAAGCT 9480
CTTCAGTAAA AGCATATTTT GCCGTTAGTG TGAAAAAAAA CAAATTTAAA AACCAACATA 9540
GAACAAATAA GCAGACAATA AAACCAAGGC GCAACACAAA CAACGCGCTT ACAATTTTCA 9600
CAAAAAAGCA ACAAGAGTAA CGTTTAGTAT TTGGATATGG TTATTGTAAT TGAGAATTTT 9660
ATAACAATTA TATTAAGGGA ATGAGTATGT TTTTAAATTC AAAACTTTCG CGCTCAGTCA 9720
AACTTGCCAT ATCCGCAGGC TTAACAGCCT CGCTAGCTAT GCCTGTTTTT GCAGAAGAAA 9780
CTGCTGCTGA AGAACAAATA GAAAGAGTCG CAGTGACCGG ATCGCGAATC GCTAAAGCAG 9840
AGCTAACTCA ACCAGCTCCA GTCGTCAGCC TTTCAGCCGA AGAACTGACA AAATTTGGTA 9900
ATCAAGATTT AGGTAGCGTA CTAGCAGAAT TACCTGCTAT TGGTGCAACC AACACTATTA 9960
TTGGTAATAA CAATAGCAAC TCAAGCGCAG GTGTTAGCTC AGCAGACTTG CGTCGTCTAG 10020
GTGCTAACAG AACCTTAGTA TTAGTCAACG GTAAGCGCTA CGTTGCCGGC CAACCGGGCT 10080
CAGCTGAGGT AGATTTGTCA ACTATACCAA CTAGCATGAT CTCGCGAGTT GAGATTGTAA 10140
CCGGCGGTGC TTCAGCAATT TATGGTTCGG ACGCTGTATC AGGTGTTATC AACGTTATCC 10200

FIG. 4A-10

TTAAAGAAGA CTTTGAAGGC TTTGAGTTTA ACGCACGTAC TAGCGGTTCT ACTGAAAGTG 10260
TAGGCACTCA AGAGCACTCT TTTGACATTT TGGGTGGTGC AAACGTTGCA GATGGACGTG 10320
GTAATGTAAC CTTCTACGCA GGTTATGAAC GTACAAAAGA AGTCATGGCT ACCGACATTC 10380
GCCAATTCGA TGCTTGGGGA ACAATTAAAA ACGAAGCCGA TGGTGGTGAA GATGATGGTA 10440
TTCCAGACAG ACTACGTGTA CCACGAGTTT ATTCTGAAAT GATTAATGCT ACCGGTGTTA 10500
TCAATGCATT TGGTGGTGGA ATTGGTCGCT CAACCTTTGA CAGTAACGGC AATCCTATTG 10560
CACAACAAGA ACGTGATGGG ACTAACAGCT TTGCATTTGG TTCATTCCCT AATGGCTGTG 10620
ACACATGTTT CAACACTGAA GCATACGAAA ACTATATTCC AGGGGTAGAA AGAATAAACG 10680
TTGGCTCATC ATTCAACTTT GATTTTACCG ATAACATTCA ATTTTACACT GACTTCAGAT 10740
ATGTAAAGTC AGATATTCAG CAACAATTTC AGCCTTCATT CCGTTTTGGT AACATTAATA 10800
TCAATGTTGA AGATAACGCC TTTTTGAATG ACGACTTGCG TCAGCAAATG CTCGATGCGG 10860
GTCAAACCAA TGCTAGTTTT GCCAAGTTTT TTGATGAATT AGGAAATCGC TCAGCAGAAA 10920
ATAAACGCGA ACTTTTCCGT TACGTAGGTG GCTTTAAAGG TGGCTTTGAT ATTAGCGAAA 10980
CCATATTTGA TTACGACCTT TACTATGTTT ATGGCGAGAC TAATAACCGT CGTAAAACCC 11040
TTAATGACCT AATTCCTGAT AACTTTGTCG CAGCTGTCGA CTCTGTTATT GATCCTGATA 11100
CTGGCTTAGC AGCGTGTCGC TCACAAGTAG CAAGCGCTCA AGGCGATGAC TATACAGATC 11160
CCGCGTCTGT AAATGGTAGC GACTGTGTTG CTTATAACCC ATTTGGCATG GGTCAAGCTT 11220

FIG. 4A-11

CAGCAGAAGC CCGCGACTGG GTTTCTGCTG ATGTGACTCG TGAAGACAAA ATAACTCAAC 11280
AAGTGATTGG TGGTACTCTC GGTACCGATT CTGAAGAACT ATTTGAGCTT CAAGGTGGTG 11340
CAATCGCTAT GGTTGTTGGT TTTGAATACC GTGAAGAAAC GTCTGGTTCA ACAACCGATG 11400
AATTTACTAA AGCAGGTTTC TTGACAAGCG CTGCAACGCC AGATTCTTAT GGCGAATACG 11460
ACGTGACTGA GTATTTTGTT GAGGTGAACA TCCCAGTACT AAAAGAATTA CCTTTTGCAC 11520
ATGAGTTGAG CTTTGACGGT GCATACCGTA ATGCTGATTA CTCACATGCC GGTAAGACTG 11580
AAGCATGGAA AGCTGGTATG TTCTACTCAC CATTAGAGCA ACTTGCATTA CGTGGTACGG 11640
TAGGTGAAGC AGTACGAGCA CCAAACATTG CAGAAGCCTT TAGTCCACGC TCTCCTGGTT 11700
TTGGCCGCGT TTCAGATCCA TGTGATGCAG ATAACATTAA TGACGATCCG GATCGCGTGT 11760
CAAACTGTGC AGCATTGGGG ATCCCTCCAG GATTCCAAGC TAATGATAAC GTCAGTGTAG 11820
ATACCTTATC TGGTGGTAAC CCAGATCTAA AACCTGAAAC ATCAACATCC TTTACAGGTG 11880
GTCTTGTTTG GACACCAACG TTTGCTGACA ATCTATCATT CACTGTCGAT TATTATGATA 11940
TTCAAATTGA GGATGCTATT TTGTCAGTAG CCACCCAGAC TGTGGCTGAT AACTGTGTTG 12000
ACTCAACTGG CGGACCTGAC ACCGACTTCT GTAGTCAAGT TGATCGTAAT CCAACGACCT 12060
ATGATATTGA ACTTGTTCGC TCTGGTTATC TAAATGCCGC GGCATTGAAT ACCAAAGGTA 12120
TTGAATTTCA AGCTGCATAC TCATTAGATC TAGAGTCTTT CAACGCGCCT GGTGAACTAC 12180
GCTTCAACCT ATTGGGGAAC CAATTACTTG AACTAGAACG TCTTGAATTC CAAAATCGTC 12240

FIG. 4A-12

CTGATGAGAT TAATGATGAA AAAGGCGAAG TAGGTGATCC AGAGCTGCAG TTCCGCCTAG 12300
GCATCGATTA CCGTCTAGAT GATCTAAGTG TTAGCTGGAA CACGCGTTAT ATTGATAGCG 12360
TAGTAACTTA TGATGTCTCT GAAAATGGTG GCTCTCCTGA AGATTTATAT CCAGGCCACA 12420
TAGGCTCAAT GACAACTCAT GACTTGAGCG CTACATACTA CATCAATGAG AACTTCATGA 12480
TTAACGGTGG TGTACGTAAC CTATTTGACG CACTTCCACC TGGATACACT AACGATGCGC 12540
TATATGATCT AGTTGGTCGC CGTGCATTCC TAGGTATTAA GGTAATGATG TAATTAATTA 12600
TTACGCCTCT AACTAATAAA AATGCAATCT CTTCGTAGAG ATTGCATTTT TTTATGAAAT 12660
CCAATCTTAA ACTGGTTCTC CGAGCATCTT ACGCCTTAAA AACCCCGCCC CTCAATGTAA 12720
CGCCAAAGTT AATTGCTTAC ACGCACTTAC ACAAACGAAC AATTTCATTA ACACGAGACA 12780
CAGCTCACGC TTTTTATTTT ACCCTTGATT TTACTACATA AAATTGCGTT TTAGCGCACA 12840
AGTGTTCTCC CAAGCTGGTC GTATCTGTAA TTATTCAGTC CCAGGTGATT GTATTGACCC 12900
ATAAGCTCAG GTAGTCTGCT CTGCCATTAG CTAAACAATA TTGACAAAAT GGCGATAAAA 12960
TGTGGCTTAG CGCTAAGTTC ACCGTAAGTT TTATCGGCAT TAAGTCCCAA CAGATTATTA 13020
ACGGAAACCC GCTAAACTGA TGGCAAAAAT AAATAGTGAA CACTTGGATG AAGCTACTAT 13080
TACTTCGAAT AAGTGTACGC AAACAGAGAC TGAGGCTCGG CATAGAAATG CCACTACAAC 13140
ACCTGAGATG CGCCGATTCA TACAAGAGTC GGATCTCAGT GTTAGCCAAC TGTCTAAAAT 13200
ATTAAATATC AGTGAAGCTA CCGTACGTAA GTGGCGCAAG CGTGACTCTG TCGAAAACTG 13260

FIG. 4A-13

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TCCTAATACC CCGCACCATC TCAATACCAC GCTAACCCCT TTGCAAGAAT ATGTGGTTGT 13320
GGGCCTGCGT TATCAATTGA AAATGCCATT AGACAGATTG CTCAAAGCAA CCCAAGAGTT 13380
TATCAATCCA AACGTGTCGC GCTCAGGTTT AGCAAGATGT TTGAAGCGTT ATGGCGTTTC 13440
ACGGGTGAGT GATATCCAAA GCCCACACGT ACCAATGCGC TACTTTAATC AAATTCCAGT 13500
CACTCAAGGC AGCGATGTGC AAACCTACAC CCTGCACTAT GAAACGCTGG CAAAAACCTT 13560
AGCCTTACCT AGTACCGATG GTGACAATGT GGTGCAAGTG GTGTCTCTCA CCATTCCACC 13620
AAAGTTAACC GAAGAAGCAC CCAGTTCAAT TTTGCTCGGC ATTGATCCTC ATAGCGACTG 13680
GATCTATCTC GACATATACC AAGATGGCAA TACACAAGCC ACGAATAGAT ATATGGCTTA 13740
TGTGCTAAAA CACGGGCCAT TCCATTTACG AAAGTTACTC GTGCGTAACT ATCACACCTT 13800
TTTACAGCGC TTTCCTGGAG CGACGCAAAA TCGCCGCCCC TCTAAAGATA TGCCTGAAAC 13860
AATCAACAAG ACGCCTGAAA CACAGGCACC CAGTGGAGAC TCATAATGAG CCAGACCTCT 13920
AAACCTACAA ACTCAGCAAC TGAGCAAGCA CAAGACTCAC AAGCTGACTC TCGTTTAAAT 13980
AAACGACTAA AAGATATGCC AATTGCTATT GTTGGCATGG CGAGTATTTT TGCAAACTCT 14040
CGCTATTTGA ATAAGTTTTG GGACTTAATC AGCGAAAAAA TTGATGCGAT TACTGAATTA 14100
CCATCAACTC ACTGGCAGCC TGAAGAATAT TACGACGCAG ATAAAACCGC AGCAGACAAA 14160
AGCTACTGTA AACGTGGTGG CTTTTTGCCA GATGTAGACT TCAACCCAAT GGAGTTTGGC 14220
CTGCCGCCAA ACATTTTGGA ACTGACCGAT TCATCGCAAC TATTATCACT CATCGTTGCT 14280
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FIG. 4A-14

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AAAGAAGTGT TGGCTGATGC TAACTTACCT GAGAATTACG ACCGCGATAA AATTGGTATC 14340
ACCTTAGGTG TCGGCGGTGG TCAAAAAATT AGCCACAGCC TAACAGCGCG TCTGCAATAC 14400
CCAGTATTGA AGAAAGTATT CGCCAATAGC GGCATTAGTG ACACCGACAG CGAAATGCTT 14460
ATCAAGAAAT TCCAAGACCA ATATGTACAC TGGGAAGAAA ACTCGTTCCC AGGTTCACTT 14520
GGTAACGTTA TTGCGGGCCG TATCGCCAAC CGCTTCGATT TTGGCGGCAT GAACTGTGTG 14580
GTTGATGCTG CCTGTGCTGG ATCACTTGCT GCTATGCGTA TGGCGCTAAC AGAGCTAACT 14640
GAAGGTCGCT CTGAAATGAT GATCACCGGT GGTGTGTGTA CTGATAACTC ACCCTCTATG 14700
TATATGAGCT TTTCAAAAAC GCCCGCCTTT ACCACTAACG AAACCATTCA GCCATTTGAT 14760
ATCGACTCAA AAGGCATGAT GATTGGTGAA GGTATTGGCA TGGTGGCGCT AAAGCGTCTT 14820
GAAGATGCAG AGCGCGATGG CGACCGCATT TACTCTGTAA TTAAAGGTGT GGGTGCATCA 14880
TCTGACGGTA AGTTTAAATC AATCTATGCC CCTCGCCCAT CAGGCCAAGC TAAAGCACTT 14940
AACCGTGCCT ATGATGACGC AGGTTTTGCG CCGCATACCT TAGGTCTAAT TGAAGCTCAC 15000
GGAACAGGTA CTGCAGCAGG TGACGCGGCA GAGTTTGCCG GCCTTTGCTC AGTATTTGCT 15060
GAAGGCAACG ATACCAAGCA ACACATTGCG CTAGGTTCAG TTAAATCACA AATTGGTCAT 15120
ACTAAATCAA CTGCAGGTAC AGCAGGTTTA ATTAAAGCTG CTCTTGCTTT GCATCACAAG 15180
GTACTGCCGC CGACCATTAA CGTTAGTCAG CCAAGCCCTA AACTTGATAT CGAAAACTCA 15240
CCGTTTTATC TAAACACTGA GACTCGTCCA TGGTTACCAC GTGTTGATGG TACGCCGCGC 15300
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FIG. 4A-15

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CGCGCGGGTA TTAGCTCATT TGGTTTTGGT GGCACTAACT TCCATTTTGT ACTAGAAGAG 15360
TACAACCAAG AACACAGCCG TACTGATAGC GAAAAAGCTA AGTATCGTCA ACGCCAAGTG 15420
GCGCAAAGCT TCCTTGTTAG CGCAAGCGAT AAAGCATCGC TAATTAACGA GTTAAACGTA 15480
CTAGCAGCAT CTGCAAGCCA AGCTGAGTTT ATCCTCAAAG ATGCAGCAGC AAACTATGGC 15540
GTACGTGAGC TTGATAAAAA TGCACCACGG ATCGGTTTAG TTGCAAACAC AGCTGAAGAG 15600
TTAGCAGGCC TAATTAAGCA AGCACTTGCC AAACTAGCAG CTAGCGATGA TAACGCATGG 15660
CAGCTACCTG GTGGCACTAG CTACCGCGCC GCTGCAGTAG AAGGTAAAGT TGCCGCACTG 15720
TTTGCTGGCC AAGGTTCACA ATATCTCAAT ATGGGCCGTG ACCTTACTTG TTATTACCCA 15780
GAGATGCGTC AGCAATTTGT AACTGCAGAT AAAGTATTTG CCGCAAATGA TAAAACGCCG 15840
TTATCGCAAA CTCTGTATCC AAAGCCTGTA TTTAATAAAG ATGAATTAAA GGCTCAAGAA 15900
GCCATTTTGA CCAATACCGC CAATGCCCAA AGCGCAATTG GTGCGATTTC AATGGGTCAA 15960
TACGATTTGT TTACTGCGGC TGGCTTTAAT GCCGACATGG TTGCAGGCCA TAGCTTTGGT 16020
GAGCTAAGTG CACTGTGTGC TGCAGGTGTT ATTTCAGCTG ATGACTACTA CAAGCTGGCT 16080
TTTGCTCGTG GTGAGGCTAT GGCAACAAAA GCACCGGCTA AAGACGGCGT TGAAGCAGAT 16140
GCAGGAGCAA TGTTTGCAAT CATAACCAAG AGTGCTGCAG ACCTTGAAAC CGTTGAAGCC 16200
ACCATCGCTA AATTTGATGG GGTGAAAGTC GCTAACTATA ACGCGCCAAC GCAATCAGTA 16260
ATTGCAGGCC CAACAGCAAC TACCGCTGAT GCGGCTAAAG CGCTAACTGA GCTTGGTTAC 16320
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FIG. 4A-16

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AAAGCGATTA ACCTGCCAGT ATCAGGTGCA TTCCACACTG AACTTGTTGG TCACGCTCAA 16380
GCGCCATTTG CTAAAGCGAT TGACGCAGCC AAATTTACTA AAACAAGCCG AGCACTTTAC 16440
TCAAATGCAA CTGGCGGACT TTATGAAAGC ACTGCTGCAA AGATTAAAGC CTCGTTTAAG 16500
AAACATATGC TTCAATCAGT GCGCTTTACT AGCCAGCTAG AAGCCATGTA CAACGACGGC 16560
GCCCGTGTAT TTGTTGAATT TGGTCCAAAG AACATCTTAC AAAAATTAGT TCAAGGCACG 16620
CTTGTCAACA CTGAAAATGA AGTTTGCACT ATCTCTATCA ACCCTAATCC TAAAGTTGAT 16680
AGTGATCTGC AGCTTAAGCA AGCAGCAATG CAGCTAGCGG TTACTGGTGT GGTACTCAGT 16740
GAAATTGACC CATACCAAGC CGATATTGCC GCACCAGCGA AAAAGTCGCC AATGAGCATT 16800
TCGCTTAATG CTGCTAACCA TATCAGCAAA GCAACTCGCG CTAAGATGGC CAAGTCTTTA 16860
GAGACAGGTA TCGTCACCTC GCAAATAGAA CATGTTATTG AAGAAAAAAT CGTTGAAGTT 16920
GAGAAACTGG TTGAAGTCGA AAAGATCGTC GAAAAAGTGG TTGAAGTAGA GAAAGTTGTT 16980
GAGGTTGAAG CTCCTGTTAA TTCAGTGCAA GCCAATGCAA TTCAAACCCG TTCAGTTGTC 17040
GCTCCAGTAA TAGAGAACCA AGTCGTGTCT AAAAACAGTA AGCCAGCAGT CCAGAGCATT 17100
AGTGGTGATG CACTCAGCAA CTTTTTTGCT GCACAGCAGC AAACCGCACA GTTGCATCAG 17160
CAGTTCTTAG CTATTCCGCA GCAATATGGT GAGACGTTCA CTACGCTGAT GACCGAGCAA 17220
GCTAAACTGG CAAGTTCTGG TGTTGCAATT CCAGAGAGTC TGCAACGCTC AATGGAGCAA 17280
TTCCACCAAC TACAAGCGCA AACACTACAA AGCCACACCC AGTTCCTTGA GATGCAAGCG 17340
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FIG. 4A-17

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GGTAGCAACA TTGCAGCGTT AAACCTACTC AATAGCAGCC AAGCAACTTA CGCTCCAGCC 17400
ATTCACAATG AAGCGATTCA AAGCCAAGTG GTTCAAAGCC AAACTGCAGT CCAGCCAGTA 17460
ATTTCAACAC AAGTTAACCA TGTGTCAGAG CAGCCAACTC AAGCTCCAGC TCCAAAAGCG 17520
CAGCCAGCAC CTGTGACAAC TGCAGTTCAA ACTGCTCCGG CACAAGTTGT TCGTCAAGCC 17580
GCACCAGTTC AAGCCGCTAT TGAACCGATT AATACAAGTG TTGCGACTAC AACGCCTTCA 17640
GCCTTCAGCG CCGAAACAGC CCTGAGCGCA ACAAAAGTCC AAGCCACTAT GCTTGAAGTG 17700
GTTGCTGAGA AAACCGGTTA CCCAACTGAA ATGCTAGAGC TTGAAATGGA TATGGAAGCC 17760
GATTTAGGCA TCGATTCTAT CAAGCGTGTA GAAATTCTTG GCACAGTACA AGATGAGCTA 17820
CCGGGTCTAC CTGAGCTTAG CCCTGAAGAT CTAGCTGAGT GTCGAACGCT AGGCGAAATC 17880
GTTGACTATA TGGGCAGTAA ACTGCCGGCT GAAGGCTCTA TGAATTCTCA GCTGTCTACA 17940
GGTTCCGCAG CTGCGACTCC TGCAGCGAAT GGTCTTTCTG CGGAGAAAGT TCAAGCGACT 18000
ATGATGTCTG TGGTTGCCGA AAAGACTGGC TACCCAACTG AAATGCTAGA GCTTGAAATG 18060
GATATGGAAG CCGATTTAGG CATAGATTCT ATCAAGCGCG TTGAAATTCT TGGCACAGTA 18120
CAAGATGAGC TACCGGGTCT ACCTGAGCTT AGCCCTGAAG ATCTAGCTGA GTGTCGTACT 18180
CTAGGCGAAA TCGTTGACTA TATGAACTCT AAACTCGCTG ACGGCTCTAA GCTGCCGGCT 18240
GAAGGCTCTA TGAATTCTCA GCTGTCTACA AGTGCCGCAG CTGCGACTCC TGCAGCGAAT 18300
GGTCTCTCTG CGGAGAAAGT TCAAGCGACT ATGATGTCTG TGGTTGCCGA AAAGACTGGC 18360
```

FIG. 4A-18

TACCCAACTG AAATGCTAGA ACTTGAAATG GATATGGAAG CTGACCTTGG CATCGATTCA 18420
ATCAAGCGCG TTGAAATTCT TGGCACAGTA CAAGATGAGC TACCGGGTTT ACCTGAGCTA 18480
AATCCAGAAG ATTTGGCAGA GTGTCGTACT CTTGGCGAAA TCGTGACTTA TATGAACTCT 18540
AAACTCGCTG ACGGCTCTAA GCTGCCAGCT GAAGGCTCTA TGCACTATCA GCTGTCTACA 18600
AGTACCGCTG CTGCGACTCC TGTAGCGAAT GGTCTCTCTG CAGAAAAAGT TCAAGCGACC 18660
ATGATGTCTG TAGTTGCAGA TAAAACTGGC TACCCAACTG AAATGCTTGA ACTTGAAATG 18720
GATATGGAAG CCGATTTAGG TATCGATTCT ATCAAGCGCG TTGAAATTCT TGGCACAGTA 18780
CAAGATGAGC TACCGGGTTT ACCTGAGCTA AATCCAGAAG ATCTAGCAGA GTGTCGCACC 18840
CTAGGCGAAA TCGTTGACTA TATGGGCAGT AAACTGCCGG CTGAAGGCTC TGCTAATACA 18900
AGTGCCGCTG CGTCTCTTAA TGTTAGTGCC GTTGCGGCGC CTCAAGCTGC TGCGACTCCT 18960
GTATCGAACG GTCTCTCTGC AGAGAAAGTG CAAAGCACTA TGATGTCAGT AGTTGCAGAA 19020
AAGACCGGCT ACCCAACTGA AATGCTAGAA CTTGGCATGG ATATGGAAGC CGATTTAGGT 19080
ATCGACTCAA TTAAACGCGT TGAGATTCTT GGCACAGTAC AAGATGAGCT ACCGGGTCTA 19140
CCAGAGCTTA ATCCTGAAGA TTTAGCTGAG TGCCGTACGC TGGGCGAAAT CGTTGACTAT 19200
ATGAACTCTA AGCTGGCTGA CGGCTCTAAG CTTCCAGCTG AAGGCTCTGC TAATACAAGT 19260
GCCACTGCTG CGACTCCTGC AGTGAATGGT CTTTCTGCTG ACAAGGTACA GGCGACTATG 19320
ATGTCTGTAG TTGCTGAAAA GACCGGCTAC CCAACTGAAA TGCTAGAACT TGGCATGGAT 19380

FIG. 4A-19

ATGGAAGCAG ACCTTGGTAT TGATTCTATT AAGCGCGTTG AAATTCTTGG CACAGTACAA 19440
GATGAGCTCC CAGGTTTACC TGAGCTTAAT CCTGAAGATC TCGCTGAGTG CCGCACGCTT 19500
GGCGAAATCG TTAGCTATAT GAACTCTCAA CTGGCTGATG GCTCTAAACT TTCTACAAGT 19560
GCGGCTGAAG GCTCTGCTGA TACAAGTGCT GCAAATGCTG CAAAGCCGGC AGCAATTTCG 19620
GCAGAACCAA GTGTTGAGCT TCCTCCTCAT AGCGAGGTAG CGCTAAAAAA GCTTAATGCG 19680
GCGAACAAGC TAGAAAATTG TTTCGCCGCA GACGCAAGTG TTGTGATTAA CGATGATGGT 19740
CACAACGCAG GCGTTTTAGC TGAGAAACTT ATTAAACAAG GCCTAAAAGT AGCCGTTGTG 19800
CGTTTACCGA AAGGTCAGCC TCAATCGCCA CTTTCAAGCG ATGTTGCTAG CTTTGAGCTT 19860
GCCTCAAGCC AAGAATCTGA GCTTGAAGCC AGTATCACTG CAGTTATCGC GCAGATTGAA 19920
ACTCAGGTTG GCGCTATTGG TGGCTTTATT CACTTGCAAC CAGAAGCGAA TACAGAAGAG 19980
CAAACGGCAG TAAACCTAGA TGCGCAAAGT TTTACTCACG TTAGCAATGC GTTCTTGTGG 20040
GCCAAATTAT TGCAACCAAA GCTCGTTGCT GGAGCAGATG CGCGTCGCTG TTTTGTAACA 20100
GTAAGCCGTA TCGACGGTGG CTTTGGTTAC CTAAATACTG ACGCCCTAAA AGATGCTGAG 20160
CTAAACCAAG CAGCATTAGC TGGTTTAACT AAAACCTTAA GCCATGAATG GCCACAAGTG 20220
TTCTGTCGCG CGCTAGATAT TGCAACAGAT GTTGATGCAA CCCATCTTGC TGATGCAATC 20280
ACCAGTGAAC TATTTGATAG CCAAGCTCAG CTACCTGAAG TGGGCTTAAG CTTAATTGAT 20340
GGCAAAGTTA ACCGCGTAAC TCTAGTTGCT GCTGAAGCTG CAGATAAAAC AGCAAAAGCA 20400

FIG. 4A-20

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GAGCTTAACA GCACAGATAA AATCTTAGTG ACTGGTGGGG CAAAAGGGGT GACATTTGAA 20460
TGTGCACTGG CATTAGCATC TCGCAGCCAG TCTCACTTTA TCTTAGCTGG GCGCAGTGAA 20520
TTACAAGCTT TACCAAGCTG GGCTGAGGGT AAGCAAACTA GCGAGCTAAA ATCAGCTGCA 20580
ATCGCACATA TTATTTCTAC TGGTCAAAAG CCAACGCCTA AGCAAGTTGA AGCCGCTGTG 20640
TGGCCAGTGC AAAGCAGCAT TGAAATTAAT GCCGCCCTAG CCGCCTTTAA CAAAGTTGGC 20700
GCCTCAGCTG AATACGTCAG CATGGATGTT ACCGATAGCG CCGCAATCAC AGCAGCACTT 20760
AATGGTCGCT CAAATGAGAT CACCGGTCTT ATTCATGGCG CAGGTGTACT AGCCGACAAG 20820
CATATTCAAG ACAAGACTCT TGCTGAACTT GCTAAAGTTT ATGGCACTAA AGTCAACGGC 20880
CTAAAAGCGC TGCTCGCGGC ACTTGAGCCA AGCAAAATTA AATTACTTGC TATGTTCTCA 20940
TCTGCAGCAG GTTTTTACGG TAATATCGGC CAAAGCGATT ACGCGATGTC GAACGATATT 21000
CTTAACAAGG CAGCGCTGCA GTTCACCGCT CGCAACCCAC AAGCTAAAGT CATGAGCTTT 21060
AACTGGGGTC CTTGGGATGG CGGCATGGTT AACCCAGCGC TTAAAAAGAT GTTTACCGAG 21120
CGTGGTGTGT ACGTTATTCC ACTAAAAGCA GGTGCAGAGC TATTTGCCAC TCAGCTATTG 21180
GCTGAAACTG GCGTGCAGTT GCTCATTGGT ACGTCAATGC AAGGTGGCAG CGACACTAAA 21240
GCAACTGAGA CTGCTTCTGT AAAAAAGCTT AATGCGGGTG AGGTGCTAAG TGCATCGCAT 21300
CCGCGTGCTG GTGCACAAAA AACACCACTA CAAGCTGTCA CTGCAACGCG TCTGTTAACC 21360
CCAAGTGCCA TGGTCTTCAT TGAAGATCAC CGCATTGGCG GTAACAGTGT GTTGCCAACG 21420
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FIG. 4A-21

```
GTATGCGCCA TCGACTGGAT GCGTGAAGCG GCAAGCGACA TGCTTGGCGC TCAAGTTAAG 21480
GTACTTGATT ACAAGCTATT AAAAGGCATT GTATTTGAGA CTGATGAGCC GCAAGAGTTA 21540
ACACTTGAGC TAACGCCAGA CGATTCAGAC GAAGCTACGC TACAAGCATT AATCAGCTGT 21600
AATGGGCGTC CGCAATACAA GGCGACGCTT ATCAGTGATA ATGCCGATAT TAAGCAACTT 21660
AACAAGCAGT TTGATTTAAG CGCTAAGGCG ATTACCACAG CAAAAGAGCT TTATAGCAAC 21720
GGCACCTTGT TCCACGGTCC GCGTCTACAA GGGATCCAAT CTGTAGTGCA GTTCGATGAT 21780
CAAGGCTTAA TTGCTAAAGT CGCTCTGCCT AAGGTTGAAC TTAGCGATTG TGGTGAGTTC 21840
TTGCCGCAAA CCCACATGGG TGGCAGTCAA CCTTTTGCTG AGGACTTGCT ATTACAAGCT 21900
ATGCTGGTTT GGGCTCGCCT TAAAACTGGC TCGGCAAGTT TGCCATCAAG CATTGGTGAG 21960
TTTACCTCAT ACCAACCAAT GGCCTTTGGT GAAACTGGTA CCATAGAGCT TGAAGTGATT 22020
AAGCACAACA AACGCTCACT TGAAGCGAAT GTTGCGCTAT ATCGTGACAA CGGCGAGTTA 22080
AGTGCCATGT TTAAGTCAGC TAAAATCACC ATTAGCAAAA GCTTAAATTC AGCATTTTTA 22140
CCTGCTGTCT TAGCAAACGA CAGTGAGGCG AATTAGTGGA ACAAACGCCT AAAGCTAGTG 22200
CGATGCCGCT GCGCATCGCA CTTATCTTAC TGCCAACACC GCAGTTTGAA GTTAACTCTG 22260
TCGACCAGTC AGTATTAGCC AGCTATCAAA CACTGCAGCC TGAGCTAAAT GCCCTGCTTA 22320
ATAGTGCGCC GACACCTGAA ATGCTCAGCA TCACTATCTC AGATGATAGC GATGCAAACA 22380
GCTTTGAGTC GCAGCTAAAT GCTGCGACCA ACGCAATTAA CAATGGCTAT ATCGTCAAGC 22440
```

FIG. 4A-22

TTGCTACGGC AACTCACGCT TTGTTAATGC TGCCTGCATT AAAAGCGGCG CAAATGCGGA 22500
TCCATCCTCA TGCGCAGCTT GCCGCTATGC AGCAAGCTAA ATCGACGCCA ATGAGTCAAG 22560
TATCTGGTGA GCTAAAGCTT GGCGCTAATG CGCTAAGCCT AGCTCAGACT AATGCGCTGT 22620
CTCATGCTTT AAGCCAAGCC AAGCGTAACT TAACTGATGT CAGCGTGAAT GAGTGTTTTG 22680
AGAACCTCAA AAGTGAACAG CAGTTCACAG AGGTTTATTC GCTTATTCAG CAACTTGCTA 22740
GCCGCACCCA TGTGAGAAAA GAGGTTAATC AAGGTGTGGA ACTTGGCCCT AAACAAGCCA 22800
AAAGCCACTA TTGGTTTAGC GAATTTCACC AAAACCGTGT TGCTGCCATC AACTTTATTA 22860
ATGGCCAACA AGCAACCAGC TATGTGCTTA CTCAAGGTTC AGGATTGTTA GCTGCGAAAT 22920
CAATGCTAAA CCAGCAAAGA TTAATGTTTA TCTTGCCGGG TAACAGTCAG CAACAAATAA 22980
CCGCATCAAT AACTCAGTTA ATGCAGCAAT TAGAGCGTTT GCAGGTAACT GAGGTTAATG 23040
AGCTTTCTCT AGAATGCCAA CTAGAGCTGC TCAGCATAAT GTATGACAAC TTAGTCAACG 23100
CAGACAAACT CACTACTCGC GATAGTAAGC CCGCTTATCA GGCTGTGATT CAAGCAAGCT 23160
CTGTTAGCGC TGCAAAGCAA GAGTTAAGCG CGCTTAACGA TGCACTCACA GCGCTGTTTG 23220
CTGAGCAAAC AAACGCCACA TCAACGAATA AAGGCTTAAT CCAATACAAA ACACCGGCGG 23280
GCAGTTACTT AACCCTAACA CCGCTTGGCA GCAACAATGA CAACGCCCAA GCGGGTCTTG 23340
CTTTTGTCTA TCCGGGTGTG GGAACGGTTT ACGCCGATAT GCTTAATGAG CTGCATCAGT 23400
ACTTCCCTGC GCTTTACGCC AAACTTGAGC GTGAAGGCGA TTTAAAGGCG ATGCTACAAG 23460

FIG. 4A-23

CAGAAGATAT CTATCATCTT GACCCTAAAC ATGCTGCCCA AATGAGCTTA GGTGACTTAG 23520
CCATTGCTGG CGTGGGGAGC AGCTACCTGT TAACTCAGCT GCTCACCGAT GAGTTTAATA 23580
TTAAGCCTAA TTTTGCATTA GGTTACTCAA TGGGTGAAGC ATCAATGTGG GCAAGCTTAG 23640
GCGTATGGCA AAACCCGCAT GCGCTGATCA GCAAAACCCA AACCGACCCG CTATTTACTT 23700
CTGCTATTTC CGGCAAATTG ACCGCGGTTA GACAAGCTTG GCAGCTTGAT GATACCGCAG 23760
CGGAAATCCA GTGGAATAGC TTTGTGGTTA GAAGTGAAGC AGCGCCGATT GAAGCCTTGC 23820
TAAAAGATTA CCCACACGCT TACCTCGCGA TTATTCAAGG GGATACCTGC GTAATCGCTG 23880
GCTGTGAAAT CCAATGTAAA GCGCTACTTG CAGCACTGGG TAAACGCGGT ATTGCAGCTA 23940
ATCGTGTAAC GGCGATGCAT ACGCAGCCTG CGATGCAAGA GCATCAAAAT GTGATGGATT 24000
TTTATCTGCA ACCGTTAAAA GCAGAGCTTC CTAGTGAAAT AAGCTTTATC AGCGCCGCTG 24060
ATTTAACTGC CAAGCAAACG GTGAGTGAGC AAGCACTTAG CAGCCAAGTC GTTGCTCAGT 24120
CTATTGCCGA CACCTTCTGC CAAACCTTGG ACTTTACCGC GCTAGTACAT CACGCCCAAC 24180
ATCAAGGCGC TAAGCTGTTT GTTGAAATTG GCGCGGATAG ACAAAACTGC ACCTTGATAG 24240
ACAAGATTGT TAAACAAGAT GGTGCCAGCA GTGTACAACA TCAACCTTGT TGCACAGTGC 24300
CTATGAACGC AAAAGGTAGC CAAGATATTA CCAGCGTGAT TAAAGCGCTT GGCCAATTAA 24360
TTAGCCATCA GGTGCCATTA TCGGTGCAAC CATTTATTGA TGGACTCAAG CGCGAGCTAA 24420
CACTTTGCCA ATTGACCAGC CAACAGCTGG CAGCACATGC AAATGTTGAC AGCAAGTTTG 24480

FIG. 4A-24

AGTCTAACCA AGACCATTTA CTTCAAGGGG AAGTCTAATG TCATTACCAG ACAATGCTTC 24540
TAACCACCTT TCTGCCAACC AGAAAGGCGC ATCTCAGGCA AGTAAAACCA GTAAGCAAAG 24600
CAAAATCGCC ATTGTCGGTT TAGCCACTCT GTATCCAGAC GCTAAAACCC CGCAAGAATT 24660
TTGGCAGAAT TTGCTGGATA AACGCGACTC TCGCAGCACC TTAACTAACG AAAAACTCGG 24720
CGCTAACAGC CAAGATTATC AAGGTGTGCA AGGCCAATCT GACCGTTTTT ATTGTAATAA 24780
AGGCGGCTAC ATTGAGAACT TCAGCTTTAA TGCTGCAGGC TACAAATTGC CGGAGCAAAG 24840
CTTAAATGGC TTGGACGACA GCTTCCTTTG GGCGCTCGAT ACTAGCCGTA ACGCACTAAT 24900
TGATGCTGGT ATTGATATCA ACGGCGCTGA TTTAAGCCGC GCAGGTGTAG TCATGGGCGC 24960
GCTGTCGTTC CCAACTACCC GCTCAAACGA TCTGTTTTTG CCAATTTATC ACAGCGCCGT 25020
TGAAAAAGCC CTGCAAGATA AACTAGGCGT AAAGGCATTT AAGCTAAGCC CAACTAATGC 25080
TCATACCGCT CGCGCGGCAA ATGAGAGCAG CCTAAATGCA GCCAATGGTG CCATTGCCCA 25140
TAACAGCTCA AAAGTGGTGG CCGATGCACT TGGCCTTGGC GGCGCACAAC TAAGCCTAGA 25200
TGCTGCCTGT GCTAGTTCGG TTTACTCATT AAAGCTTGCC TGCGATTACC TAAGCACTGG 25260
CAAAGCCGAT ATCATGCTAG CAGGCGCAGT ATCTGGCGCG GATCCTTTCT TTATTAATAT 25320
GGGATTCTCA ATCTTCCACG CCTACCCAGA CCATGGTATC TCAGTACCGT TTGATGCCAG 25380
CAGTAAAGGT TTGTTTGCTG GCGAAGGCGC TGGCGTATTA GTGCTTAAAC GTCTTGAAGA 25440
TGCCGAGCGC GACAATGACA AAATCTATGC GGTTGTTAGC GGCGTAGGTC TATCAAACGA 25500

FIG. 4A-25

CGGTAAAGGC CAGTTTGTAT TAAGCCCTAA TCCAAAAGGT CAGGTGAAGG CCTTTGAACG 25560
TGCTTATGCT GCCAGTGACA TTGAGCCAAA AGACATTGAA GTGATTGAGT GCCACGCAAC 25620
AGGCACACCG CTTGGCGATA AAATTGAGCT CACTTCAATG GAAACCTTCT TTGAAGACAA 25680
GCTGCAAGGC ACCGATGCAC CGTTAATTGG CTCAGCTAAG TCTAACTTAG GCCACCTATT 25740
AACTGCAGCG CATGCGGGGA TCATGAAGAT GATCTTCGCC ATGAAAGAAG GTTACCTGCC 25800
GCCAAGTATC AATATTAGTG ATGCTATCGC TTCGCCGAAA AAACTCTTCG GTAAACCAAC 25860
CCTGCCTAGC ATGGTTCAAG GCTGGCCAGA TAAGCCATCG AATAATCATT TTGGTGTAAG 25920
AACCCGTCAC GCAGGCGTAT CGGTATTTGG CTTTGGTGGC TGTAACGCCC ATCTGTTGCT 25980
TGAGTCATAC AACGGCAAAG GAACAGTAAA GGCAGAAGCC ACTCAAGTAC CGCGTCAAGC 26040
TGAGCCGCTA AAAGTGGTTG GCCTTGCCTC GCACTTTGGG CCTCTTAGCA GCATTAATGC 26100
ACTCAACAAT GCTGTGACCC AAGATGGGAA TGGCTTTATC GAACTGCCGA AAAAGCGCTG 26160
GAAAGGCCTT GAAAAGCACA GTGAACTGTT AGCTGAATTT GGCTTAGCAT CTGCGCCAAA 26220
AGGTGCTTAT GTTGATAACT TCGAGCTGGA CTTTTTACGC TTTAAACTGC CGCCAAACGA 26280
AGATGACCGT TTGATCTCAC AGCAGCTAAT GCTAATGCGA GTAACAGACG AAGCCATTCG 26340
TGATGCCAAG CTTGAGCCGG GGCAAAAAGT AGCTGTATTA GTGGCAATGG AAACTGAGCT 26400
TGAACTGCAT CAGTTCCGCG GCCGGGTTAA CTTGCATACT CAATTAGCGC AAAGTCTTGC 26460
CGCCATGGGC GTGAGTTTAT CAACGGATGA ATACCAAGCG CTTGAAGCCA TCGCCATGGA 26520

FIG. 4A-26

CAGCGTGCTT GATGCTGCCA AGCTCAATCA GTACACCAGC TTTATTGGTA ATATTATGGC 26580
GTCACGCGTG GCGTCACTAT GGGACTTTAA TGGCCCAGCC TTCACTATTT CAGCAGCAGA 26640
GCAATCTGTG AGCCGCTGTA TCGATGTGGC GCAAAACCTC ATCATGGAGG ATAACCTAGA 26700
TGCGGTGGTG ATTGCAGCGG TCGATCTCTC TGGTAGCTTT GAGCAAGTCA TTCTTAAAAA 26760
TGCCATTGCA CCTGTAGCCA TTGAGCCAAA CCTCGAAGCA AGCCTTAATC CAACATCAGC 26820
AAGCTGGAAT GTCGGTGAAG GTGCTGGCGC GGTCGTGCTT GTTAAAAATG AAGCTACATC 26880
GGGCTGCTCA TACGGCCAAA TTGATGCACT TGGCTTTGCT AAAACTGCCG AAACAGCGTT 26940
GGCTACCGAC AAGCTACTGA GCCAAACTGC CACAGACTTT AATAAGGTTA AAGTGATTGA 27000
AACTATGGCA GCGCCTGCTA GCCAAATTCA ATTAGCGCCA ATAGTTAGCT CTCAAGTGAC 27060
TCACACTGCT GCAGAGCAGC GTGTTGGTCA CTGCTTTGCT GCAGCGGGTA TGGCAAGCCT 27120
ATTACACGGC TTACTTAACT TAAATACTGT AGCCCAAACC AATAAAGCCA ATTGCGCGCT 27180
TATCAACAAT ATCAGTGAAA ACCAATTATC ACAGCTGTTG ATTAGCCAAA CAGCGAGCGA 27240
ACAACAAGCA TTAACCGCGC GTTTAAGCAA TGAGCTTAAA TCCGATGCTA AACACCAACT 27300
GGTTAAGCAA GTCACCTTAG GTGGCCGTGA TATCTACCAG CATATTGTTG ATACACCGCT 27360
TGCAAGCCTT GAAAGCATTA CTCAGAAATT GGCGCAAGCG ACAGCATCGA CAGTGGTCAA 27420
CCAAGTTAAA CCTATTAAGG CCGCTGGCTC AGTCGAAATG GCTAACTCAT TCGAAACGGA 27480
AAGCTCAGCA GAGCCACAAA TAACAATTGC AGCACAACAG ACTGCAAACA TTGGCGTCAC 27540

FIG. 4A-27

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CGCTCAGGCA ACCAAACGTG AATTAGGTAC CCCACCAATG ACAACAAATA CCATTGCTAA 27600
TACAGCAAAT AATTTAGACA AGACTCTTGA GACTGTTGCT GGCAATACTG TTGCTAGCAA 27660
GGTTGGCTCT GGCGACATAG TCAATTTTCA ACAGAACCAA CAATTGGCTC AACAAGCTCA 27720
CCTCGCCTTT CTTGAAAGCC GCAGTGCGGG TATGAAGGTG GCTGATGCTT TATTGAAGCA 27780
ACAGCTAGCT CAAGTAACAG GCCAAACTAT CGATAATCAG GCCCTCGATA CTCAAGCCGT 27840
CGATACTCAA ACAAGCGAGA ATGTAGCGAT TGCCGCAGAA TCACCAGTTC AAGTTACAAC 27900
ACCTGTTCAA GTTACAACAC CTGTTCAAAT CAGTGTTGTG GAGTTAAAAC CAGATCACGC 27960
TAATGTGCCA CCATACACGC CGCCAGTGCC TGCATTAAAG CCGTGTATCT GGAACTATGC 28020
CGATTTAGTT GAGTACGCAG AAGGCGATAT CGCCAAGGTA TTTGGCAGTG ATTATGCCAT 28080
TATCGACAGC TACTCGCGCC GCGTACGTCT ACCGACCACT GACTACCTGT TGGTATCGCG 28140
CGTGACCAAA CTTGATGCGA CCATCAATCA ATTTAAGCCA TGCTCAATGA CCACTGAGTA 28200
CGACATCCCT GTTGATGCGC CGTACTTAGT AGACGGACAA ATCCCTTGGG CGGTAGCAGT 28260
AGAATCAGGC CAATGTGACT TGATGCTTAT TAGCTATCTC GGTATCGACT TTGAGAACAA 28320
AGGCGAGCGG GTTTATCGAC TACTCGATTG TACCCTCACC TTCCTAGGCG ACTTGCCACG 28380
TGGCGGAGAT ACCCTACGTT ACGACATTAA GATCAATAAC TATGCTCGCA ACGGCGACAC 28440
CCTGCTGTTC TTCTTCTCGT ATGAGTGTTT TGTTGGCGAC AAGATGATCC TCAAGATGGA 28500
TGGCGGCTGC GCTGGCTTCT TCACTGATGA AGAGCTTGCC GACGGTAAAG GCGTGATTCG 28560
```

FIG. 4A-28

CACAGAAGAA GAGATTAAAG CTCGCAGCCT AGTGCAAAAG CAACGCTTTA ATCCGTTACT 28620
AGATTGTCCT AAAACCCAAT TTAGTTATGG TGATATTCAT AAGCTATTAA CTGCTGATAT 28680
TGAGGGTTGT TTTGGCCCAA GCCACAGTGG CGTCCACCAG CCGTCACTTT GTTTCGCATC 28740
TGAAAAATTC TTGATGATTG AACAAGTCAG CAAGGTTGAT CGCACTGGCG GTACTTGGGG 28800
ACTTGGCTTA ATTGAGGGTC ATAAGCAGCT TGAAGCAGAC CACTGGTACT TCCCATGTCA 28860
TTTCAAGGGC GACCAAGTGA TGGCTGGCTC GCTAATGGCT GAAGGTTGTG GCCAGTTATT 28920
GCAGTTCTAT ATGCTGCACC TTGGTATGCA TACCCAAACT AAAAATGGTC GTTTCCAACC 28980
TCTTGAAAAC GCCTCACAGC AAGTACGCTG TCGCGGTCAA GTGCTGCCAC AATCAGGCGT 29040
GCTAACTTAC CGTATGGAAG TGACTGAAAT CGGTTTCAGT CCACGCCCAT ATGCTAAAGC 29100
TAACATCGAT ATCTTGCTTA ATGGCAAAGC GGTAGTGGAT TTCCAAAACC TAGGGGTGAT 29160
GATAAAAGAG GAAGATGAGT GTACTCGTTA TCCACTTTTG ACTGAATCAA CAACGGCTAG 29220
CACTGCACAA GTAAACGCTC AAACAAGTGC GAAAAAGGTA TACAAGCCAG CATCAGTCAA 29280
TGCGCCATTA ATGGCACAAA TTCCTGATCT GACTAAAGAG CCAAACAAGG GCGTTATTCC 29340
GATTTCCCAT GTTGAAGCAC CAATTACGCC AGACTACCCG AACCGTGTAC CTGATACAGT 29400
GCCATTCACG CCGTATCACA TGTTTGAGTT TGCTACAGGC AATATCGAAA ACTGTTTCGG 29460
GCCAGAGTTC TCAATCTATC GCGGCATGAT CCCACCACGT ACACCATGCG GTGACTTACA 29520
AGTGACCACA CGTGTGATTG AAGTTAACGG TAAGCGTGGC GACTTTAAAA AGCCATCATC 29580

FIG. 4A-29

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GTGTATCGCT GAATATGAAG TGCCTGCAGA TGCGTGGTAT TTCGATAAAA ACAGCCACGG 29640
CGCAGTGATG CCATATTCAA TTTTAATGGA GATCTCACTG CAACCTAACG GCTTTATCTC 29700
AGGTTACATG GGCACAACCC TAGGCTTCCC TGGCCTTGAG CTGTTCTTCC GTAACTTAGA 29760
CGGTAGCGGT GAGTTACTAC GTGAAGTAGA TTTACGTGGT AAAACCATCC GTAACGACTC 29820
ACGTTTATTA TCAACAGTGA TGGCCGGCAC TAACATCATC CAAAGCTTTA GCTTCGAGCT 29880
AAGCACTGAC GGTGAGCCTT TCTATCGCGG CACTGCGGTA TTTGGCTATT TTAAAGGTGA 29940
CGCACTTAAA GATCAGCTAG GCCTAGATAA CGGTAAAGTC ACTCAGCCAT GGCATGTAGC 30000
TAACGGCGTT GCTGCAAGCA CTAAGGTGAA CCTGCTTGAT AAGAGCTGCC GTCACTTTAA 30060
TGCGCCAGCT AACCAGCCAC ACTATCGTCT AGCCGGTGGT CAGCTGAACT TTATCGACAG 30120
TGTTGAAATT GTTGATAATG GCGGCACCGA AGGTTTAGGT TACTTGTATG CCGAGCGCAC 30180
CATTGACCCA AGTGATTGGT TCTTCCAGTT CCACTTCCAC CAAGATCCGG TTATGCCAGG 30240
CTCCTTAGGT GTTGAAGCAA TTATTGAAAC CATGCAAGCT TACGCTATTA GTAAAGACTT 30300
GGGCGCAGAT TTCAAAAATC CTAAGTTTGG TCAGATTTTA TCGAACATCA AGTGGAAGTA 30360
TCGCGGTCAA ATCAATCCGC TGAACAAGCA GATGTCTATG GATGTCAGCA TTACTTCAAT 30420
CAAAGATGAA GACGGTAAGA AAGTCATCAC AGGTAATGCC AGCTTGAGTA AAGATGGTCT 30480
GCGCATATAC GAGGTCTTCG ATATAGCTAT CAGCATCGAA GAATCTGTAT AAATCGGAGT 30540
GACTGTCTGG CTATTTTACT CAATTTCTGT GTCAAAAGTG CTCACCTATA TTCATAGGCT 30600
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FIG. 4A-30

GCGCGCTTTT TTCTGGAAAT TGAGCAAAAG TATCTGCGTC CTAACTCGAT TTATAAGAAT 30660
GGTTTAATTG AAAAGAACAA CAGCTAAGAG CCGCAAGCTC AATATAAATA ATTAAGGGTC 30720
TTACAAATAA TGAATCCTAC AGCAACTAAC GAAATGCTTT CTCCGTGGCC ATGGGCTGTG 30780
ACAGAGTCAA ATATCAGTTT TGACGTGCAA GTGATGGAAC AACAACTTAA AGATTTTAGC 30840
CGGGCATGTT ACGTGGTCAA TCATGCCGAC CACGGCTTTG GTATTGCGCA AACTGCCGAT 30900
ATCGTGACTG AACAAGCGGC AAACAGCACA GATTTACCTG TTAGTGCTTT TACTCCTGCA 30960
TTAGGTACCG AAAGCCTAGG CGACAATAAT TTCCGCCGCG TTCACGGCGT TAAATACGCT 31020
TATTACGCAG GCGCTATGGC AAACGGTATT TCATCTGAAG AGCTAGTGAT TGCCCTAGGT 31080
CAAGCTGGCA TTTTGTGTGG TTCGTTTGGA GCAGCCGGTC TTATTCCAAG TCGCGTTGAA 31140
GCGGCAATTA ACCGTATTCA AGCAGCGCTG CCAAATGGCC CTTATATGTT TAACCTTATC 31200
CATAGTCCTA GCGAGCCAGC ATTAGAGCGT GGCAGCGTAG AGCTATTTTT AAAGCATAAG 31260
GTACGCACCG TTGAAGCATC AGCTTTCTTA GGTCTAACAC CACAAATCGT CTATTACCGT 31320
GCAGCAGGAT TGAGCCGAGA CGCACAAGGT AAAGTTGTGG TTGGTAACAA GGTTATCGCT 31380
AAAGTAAGTC GCACCGAAGT GGCTGAAAAG TTTATGATGC CAGCGCCCGC AAAAATGCTA 31440
CAAAAACTAG TTGATGACGG TTCAATTACC GCTGAGCAAA TGGAGCTGGC GCAACTTGTA 31500
CCTATGGCTG ACGACATCAC TGCAGAGGCC GATTCAGGTG GCCATACTGA TAACCGTCCA 31560
TTAGTAACAT TGCTGCCAAC CATTTTAGCG CTGAAAGAAG AAATTCAAGC TAAATACCAA 31620

FIG. 4A-31

TACGACACTC CTATTCGTGT CGGTTGTGGT GGCGGTGTGG GTACGCCTGA TGCAGCGCTG 31680
GCAACGTTTA ACATGGGCGC GGCGTATATT GTTACCGGCT CTATCAACCA AGCTTGTGTT 31740
GAAGCGGGCG CAAGTGATCA CACTCGTAAA TTACTTGCCA CCACTGAAAT GGCCGATGTG 31800
ACTATGGCAC CAGCTGCAGA TATGTTCGAG ATGGGCGTAA AACTGCAGGT GGTTAAGCGC 31860
GGCACGCTAT TCCCAATGCG CGCTAACAAG CTATATGAGA TCTACACCCG TTACGATTCA 31920
ATCGAAGCGA TCCCATTAGA CGAGCGTGAA AAGCTTGAGA AACAAGTATT CCGCTCAAGC 31980
CTAGATGAAA TATGGGCAGG TACAGTGGCG CACTTTAACG AGCGCGACCC TAAGCAAATC 32040
GAACGCGCAG AGGGTAACCC TAAGCGTAAA ATGGCATTGA TTTTCCGTTG GTACTTAGGT 32100
CTTTCTAGTC GCTGGTCAAA CTCAGGCGAA GTGGGTCGTG AAATGGATTA TCAAATTTGG 32160
GCTGGCCCTG CTCTCGGTGC ATTTAACCAA TGGGCAAAAG GCAGTTACTT AGATAACTAT 32220
CAAGACCGAA ATGCCGTCGA TTTGGCAAAG CACTTAATGT ACGGCGCGGC TTACTTAAAT 32280
CGTATTAACT CGCTAACGGC TCAAGGCGTT AAAGTGCCAG CACAGTTACT TCGCTGGAAG 32340
CCAAACCAAA GAATGGCCTA ATACACTTAC AAAGCACCAG TCTAAAAAGC CACTAATCTT 32400
GATTAGTGGC TTTTTTTATT GTGGTCAATA TGAGGCTATT TAGCCTGTAA GCCTGAAAAT 32460
ATCAGCACTC TGACTTTACA AGCAAATTAT AATTAAGGCA GGGCTCTACT CATTTATACT 32520
GCTAGCAAAC AAGCAAGTTG CCCAGTAAAA CAACAAGGTA CCTGATTTAT ATCGTCATAA 32580
AAGTTGGCTA GAGATTCGTT ATTGATCTTT ACTGATTAGA GTCGCTCTGT TTGGAAAAAG 32640

FIG. 4A-32

```
GTTTCTCGTT ATCATCAAAA TACACTCTCA AACCTTTAAT CAATTACAAC TTAGGCTTTC 32700
TGCGGGCATT TTTATCTTAT TTGCCACAGC TGTATTTGCC TTTAGGTTTT GGGTGCAACT 32760
ACCATTAATT GAGGCCTCAT TAGTTAAATT ATCTGAGCAA GAGCTCACCT CTTTAAATTA 32820
CGCTTTTCAG CAAATGAGAA AGCCACTACA AACCATTAAT TACGACTATG CGGTGTGGGA 32880
CAGAACCTAC AGCTATATGA AATCAAACTC AGCGAGCGCT AAAAGGTACT ATGAAAAACA 32940
TGAGTACCCA GATGATACGT TCAAGAGTTT AAAAGTCGAC GGAGTATTTA TATTCAACCG 33000
TACAAATCAG CCAGTTTTTA GTAAAGGTTT TAATCATAGA AATGATATAC CGCTGGTCTT 33060
TGAATTAACT GACTTTAAAC AACATCCACA AAACATCGCA TTATCTCCAC AAACCAAACA 33120
GGCACACCCA CCGGCAAGTA AGCCGTTAGA CTCCCCTGAT GATGTGCCTT CTACCCATGG 33180
GGTTATCGCC ACACGATACG GTCCAGCAAT TTATAGCTCT ACCAGCATTT TAAAATCTGA 33240
TCGTAGCGGC TCCCAACTTG GTTATTTAGT CTTCATTAGG TTAATTGATG AATGGTTCAT 33300
CGCTGAGCTA TCGCAATACA CTGCCGCAGG TGTTGAAATC GCTATGGCTG ATGCCGCAGA 33360
CGCACAATTA GCGAGATTAG GCGCAAACAC TAAGCTTAAT AAAGTAACCG CTACATCCGA 33420
ACGGTTAATA ACTAATGTCG ATGGTAAGCC TCTGTTGAAG TTAGTGCTTT ACCATACCAA 33480
TAACCAACCG CCGCCGATGC TAGATTACAG TATAATAATT CTATTAGTTG AGATGTCATT 33540
TTTACTGATC CTCGCTTATT TCCTTTACTC CTACTTCTTA GTCAGGCCAG TTAGAAAGCT 33600
GGCTTCAGAT ATTAAAAAAA TGGATAAAAG TCGTGAAATT AAAAAGCTAA GGTATCACTA 33660
```

FIG. 4A-33

CCCTATTACT GAGCTAGTCA AAGTTGCGAC TCACTTCAAC GCCCTAATGG GGACGATTCA 33720
GGAACAAACT AAACAGCTTA ATGAACAAGT TTTTATTGAT AAATTAACCA ATATTCCCAA 33780
TCGTCGCGCT TTTGAGCAGC GACTTGAAAC CTATTGCCAA CTGCTAGCCC GGCAACAAAT 33840
TGGCTTTACT CTCATCATTG CCGATGTGGA TCATTTTAAA GAGTACAACG ATACTCTTGG 33900
GCACCTTGCT GGGGATGAAG CATTAATAAA AGTGGCACAA ACACTATCGC AACAGTTTTA 33960
CCGTGCAGAA GATATTTGTG CCCGTTTTGG TGGTGAAGAA TTTATTATGT TATTTCGAGA 34020
CATACCTGAT GAGCCCTTGC AGAGAAAGCT CGATGCGATG CTGCACTCTT TTGCAGAGCT 34080
CAACCTACCT CATCCAAACT CATCAACCGC TAATTACGTT ACTGTGAGCC TTGGGGTTTG 34140
CACAGTTGTT GCTGTTGATG ATTTTGAATT TAAAAGTGAG TCGCATATTA TTGGCAGTCA 34200
GGCTGCATTA ATCGCAGATA AGGCGCTTTA TCATGCTAAA GCCTGTGGTC GTAACCAGTT 34260
GTCAAAAACT ACTATTACTG TTGATGAGAT TGAGCAATTA GAAGCAAATA AAATCGGTCA 34320
TCAAGCCTAA ACTCGTTCGA GTACTTTCCC CTAAGTCAGA GCTATTTGCC ACTTCAAGAT 34380
GTGGCTACAA GGCTTACTCT TTCAAAACCT GCATCAATAG AACACAGCAA AATACAATAA 34440
TTTAAGTCAA TTTAGCCTAT TAAACAGAGT TAATGACAGC TCATGGTCGC AACTTATTAG 34500
CTATTTCTAG CAATATAAAA ACTTATCCAT TAGTAGTAAC CAATAAAAAA ACTAATATAT 34560
AAAACTATTT AATCATTATT TTACAGATGA TTAGCTACCA CCCACCTTAA GCTGGCTATA 34620
TTCGCACTAG TAAAAATAAA CATTAGATCG GGTTCAGATC AATTTACGAG TCTCGTATAA 34680

FIG. 4A-34

AATGTACAAT AATTCACTTA ATTTAATACT GCATATTTTT ACAAGTAGAG AGCGGTGATG 34740
AAACAAAATA CGAAAGGCTT TACATTAATT GAATTAGTCA TCGTGATTAT TATTCTCGGT 34800
ATACTTGCTG CTGTGGCACT GCCGAAATTC ATCAATGTTC AAGATGACGC TAGGATCTCT 34860
GCGATGAGCG GTCAGTTTTC ATCATTTGAA AGTGCCGTAA AACTATACCA TAGCGGTTGG 34920
TTAGCCAAAG GCTACAACAC TGCGGTTGAA AAGCTCTCAG GCTTTGGCCA AGGTAATGTT 34980
GCATCAAGTG ACACAGGTTT TCCGTACTCA ACATCAGGCA CGAGTACTGA TGTGCATAAA 35040
GCTTGTGGTG AACTATGGCA TGGCATTACC GATACAGACT TCACAATTGG TGCGGTTAGT 35100
GATGGCGATC TAATGACTGC AGATGTCGAT ATTGCTTACA CCTATCGTGG TGATATGTGT 35160
ATCTATCGCG ATCTGTATTT TATTCAGCGC TCATTACCTA CTAAGGTGAT GAACTACAAA 35220
TTTAAAACTG GTGAAATAGA AATTATTGAT GCTTTCTACA ACCCTGACGG CTCAACTGGT 35280
CAATTACCAT AAATTTGGCG CTTATCTAAG TTGTACTTGC TCTGACCGAC ACAAATAATG 35340
TCGTTTCTCA GCATATATCA AAATACACAG CAAAAATTTG GGGTTAGCTA TATAGCTAAC 35400
CCCAAATCAT ATCTAACTTT ACACTGCATC TAATTCCAAA CAGTATCCAG CCAAAAGCCT 35460
AAACTATTGT TGACTCAGCG CTAAAATATG CGATGCAACA AACAAGTCTT GGATCGCAAT 35520
ACCTGAGCTA TCAAAAATGG TCACCTCATC AGCACTTTGA CGTCCTGTTG CGGACTCGTT 35580
TATCACCTGA CCAATCTCAA TTATCGGCGT ATTTCTGCTA TGTTGAAACT CACCAATAAC 35640
AATAGATTGA GAAGCAAAGT CGCAAAACAA GCGAGCATGA CTATATAGGT CAGTTGGCAA 35700

FIG. 4A-35

CTCTTGCTTA CCCACTTTAT CAGCGCCCAT TGCAGAAATA TGCGTTCCTG CTTGTACCCA 35760
CTGCGCTTCA AATAAAGGCG CTTGAGCTGT GGTTGCTGTG ATAATAATAT CTGCTTGTTC 35820
ACAAGCAGCT TGTGCATCAC AAGCTTCGGC ATTAATGCCT TTTTCTAATA AACGCTTAAC 35880
CAAGTTTTCA GTTTTGCTAG CACTACGGCC AACTACCAAT ACCTTAGTTA ATGAACGAAC 35940
CTTGCTCACT GCTAGCACTT CATATTCAGC CTGATGACCG GTACCAAAAA CAGTTAATAC 36000
CGTAGCATCT TCTCTCGCGA GGTAACTCAC TGCTACTGCA TCGGCAGCAC CAGTGCGGTA 36060
AGCATTAACG GTAGTGGCAG CAATCACCGN CTGCAACATA CCGGTTAATG GATCGAGTAA 36120
AAATACGTTA GTGCCGTGGC ATGGTAAACC ATGTTTATGG TTATCAGGCC AATAGCTGCC 36180
TGTTTTCCAG CCGACAAGGT TTGGCGTTGA AGCCGACTTT AATGAGAACA TTTCATTAAG 36240
GTTCGCGCCC TGTGCATTAA CTACCGGGAA CAAGGTTGCT TTATCATCTA CGGCAGCGAC 36300
AAACGCTTCT TTAACAGCGA TATAAGCCAG CTCATGGGAG ATGAGCTTTG ATGTTTGCGC 36360
TTCAGTTAAA TAGATCATAT TACCACCCCT GCACTCGATT CCAGATCTCA TAGCCACCAT 36420
TATCACCATC AGTATCAAAT ACATGGTACT GAGCGTGCAT TGAAGCTGTT GCACAGGCGT 36480
GGTTCGGCAA AATATGTAGA CGACTACCTA CCGGGAACTG CGCTAAATCA ATAACGCCGC 36540
CATCAACTGC TTCAATAATG CCGTGCTCTT GATTAACAGT TATAACCTGT AGACCTGATA 36600
ACACGTGACC GCTGTCGTCA CACACTAAAC CATAACCACA ATCTTTTGGC TGCTCTGCAG 36660
TACCTCTATC ACCCGAAAGA GCCATCCAAC CCGCATCAAT GAAAATCCAG TTTTTATCAG 36720

FIG. 4A-36

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GATTATGACC AATAACACTG GTCACTACCG TTGCGGCAAT ATCAGTTAAC TGACACACGT 36780
TTAGCCCTGC CATGACTAAA TCGAAGAAGG TGTACACACC CGCTCTAACC TCGGTGATCC 36840
CATCAAGGTT TTGATAGCTT TGCGCTGTTG GTGTTGAACC AATACTAACG ATGTCACATT 36900
GCATACCCGC TGCGCGAATG CGTCAGCAGC TTGTACAGCC GCTGCAACTT CATTTTGCGC 36960
CGCATCAATT AATTGCTGTT TTTCAAAACA TTGATATGAC TCACCAGCGT GAGTNAGTAC 37020
GCCGTGAAAA CTCGCTGCGC CAGACGTTAG TATCTGAGCA ATTTCAATCA ACTTATCGGC 37080
TTCCGGTGGA ATACCACCAC GATGGCCATC ACAATCAATT TCAATTAATG CTGGTATTTG 37140
GCAGTCATAA GAACCACAGA AATGATTTAG CTGATGCGCT TGCTCAACAC TATCAAGTAA 37200
AACTCTTGCA TTAATACCTT GGTCCAACAT TTTAGCAATA CGCGGCAACT TACCATCGGC 37260
AATACCTACT GCATAAATAA TGTCTGTGTA ACCTTTAGAT GCTAAGGCCT CGGCCTCTTT 37320
TACCGTTGAT ACAGTGACTG GTGAGTTTTT AGTGGGTAAT AAAAACTCGG CTGCTTCAAG 37380
TGATCTTAAC GTTTTAAAAT GCGGTCTTAG GTTTGCACCT AATCCTTCAA TTTTTTGGCG 37440
TAGTTGACTG AGGTTATTAA TAAATACTGG CTTATTTACA TATAAAAACG GTGTATCAAT 37500
TGCTTGATAC TGACTTTGCT GAGTCGTGGA AAGTATTTGA GTAGATGGCA TCTTTAATAT 37560
CCTAGTTCAT CAATCAATCT AACAAGTTTG ATGCCTAGCC ACAGTGGCTT GTATTCATGA 37620
TGCTTTGGAA AATGCTTATA TTCAAAGTAT TTGAAAGACA TCAAACTTCT TGTTTAATGC 37680
TCAGTATCCA CCAGCACGCA TTTATTTTAT ATTAACTATT ATCAAGATAT AGATTAGGTT 37740
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FIG. 4A-37

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CAAACCAAAT GATTAGTACT GAAGATCTAC GTTTTATCAG CGTAATCGCC AGTCATCGCA 37800
CCTTAGCTGA TGCCGCTAGA ACACTAAATA TCACGCCACC ATCAGTGACA TTAAGGTTGC 37860
AGCATATTGA AAAGAAACTA TCGATTAGCC TGATC                            37895
```

FIG. 4A-38

6121
*
MKQTLMAISI MSLFSFNALA AQHEHDHITV DYEGKAATEH
TIAHNQAVAK TLNFADTRAF EQSSKNLVAK FDKATADILR
AEFAFISDEI PDSVNPSLYR QAQLNMVPNG YKVSDGIYQV
RGTDLSNLTL IRSDNGWIAY DVLLTKEAAK ASLQFALKNL
PKDGDPVVAM IYSHSHADHF GGARGVQEMF PDVKVYGSDN
ITKEIVDENV LAGNAMSRRA AYQYGATLGK HDHGIVDAAL
GKGLSKGEIT YVAPDYTLNS EGKWETLTID GLEMVFMDAS
GTEAESEMIT YIPSKKALWT AELTYQGMHN IYTLRGAKVR
DALKWSKDIN EMINAFGQDV EVLFASHSAP VWGNQAINDF
LRLQRDNYGL VHNQTLRLAN DGVGIQDIGD AIQDTIPESI
YKTWHTNGYH GTYSHNAKAV YNKYLGYFD MNPANLNPLP
TKQESAKFVE YMGGADAAIK RAKDDYAQGE YRFVATALNK
VVMAEPENDS ARQLLADTYE QLGYQAEGAG WRNIYLTGAQ
ELRVGIQAGA PKTASADVIS EMDMPTLFDF LAVKIDSQQA
AKHGLVKMNV ITPDTKDILY IELSNGNLSN AVVDKEQAAD
ANLMVNKADV NRILLGQVTL KALLASGDAK LTGDKTAFSK
IADSMVEFTP DFEIVPTPVK
*
8103

FIG. 4B

8186

*STKASARVVA KFNVEEAAIS IQQCQGISLA FRYSDDLHGL
LCHWNDAANM QQEKAEILGL GSKQPEANPK NSSSELLALG
IDQKLLVQRQ NLQHEVKHDA IADSIDVCHS LSKPANVGLF
TESLASFDFA FSKLSLALGL GKAKIYSEKL AWLDFFRDRQ
LAEPLALLAR KESESFYHSL ISHINTSNRC REIDVGFEIS
ASDTEEKSAQ SAGKNDATCI GVLLWDGSHS VNFHVGTQAF
QADSLRPKGK DGYEFRWENP RIESHQSLLA RLYGRVM*

9016

FIG. 4C

8186

*GCTAGTCTTA GCTGASRTHR YSAASRAGCT CGAACAACAG CTTTAAAATT
CACTTCTTCT GCTGCAATAC TTATTTGCTG ACACTGACCA ATACTCAGTG
CAAAACGATA ACTATCATCA AGATGGAAAR GVAVAAAYSH ASNVAGGAAA
ASRGNGNCYS GNGYSRAAHA RGTYRSRASA SHSCCCAGTA AACAATGCCA
ATTATCAGCA GCGTTCATTT GCTGTTCTTT AGCCTCAATC AAACCTAAAC
CAGACTTTTG TGGCTCAGCG TTAGGCTTAT TAGGYCYSHS TRASNASAAA
AASNMTGNGN GYSAAGGYGY SRYSGNRGAA ASNRYSASNS RAACTCGACT
CTAGTAAAGC AAGACCAATA TCTTGTTTTA ACAAAACCTG TCGCTGATTA
AGTTGATGCT CAACCTTGTG ATCCGCAATA GCATCGGAAA TSRSRGAAGY
ASGNYSVAGN ARGGNASNGN HSGVAYSHSA SAAAAASSRA TCAACACAAT
GGCTCAAGCT TTTAGGTGCA TTAACTCCAA GAAAAGTTTC GCTCAGTGCA
GAGAAGTCAA ACGCAAAAGA TTTTAGCGAT AATGCCAGCA SVACYSHSSR
SRYSRAAASN VAGYHTHRGS RAASRHASHA AHSRYSSRAA CCAAGTCCTT
TCGCTTTAAT GTAAGACTCC TTGAGCGCCC ACAAATCAAA AAAGCGGTCT
CGCTGCAAGG CCTCTGGTAA CGCTAACAAG GCTCGCTTTT GYGYYSAAYS
TYRSRGYSAA TRASHHARGA SARGGNAAGR AAAAARGYSG CTGATTCAGA
GAAATAATGA CTAAGAATAG AGTGGATATT GGTGCTGTTA CGGCAACGCT
CAATGTCGAC GCCAAACTCA ATACTAGCAG AGTCAGTTTC SRGSRHTYRH
SSRSRHSASN THRSRASNAR GCYSARGGAS VAGYHGSRAA SRASTHRGCT
CCTTGCTTGC CTGACTGGCG CCTTTATTAT CAGCAGTGCA AATGCCTACT
AATAGCCAAT CTCCACTATG ACTCACATTA AAGTGGACCC CGGTTTGAGY
SSRAAGNSRA AGYYSASNAS AATHRCYSGY VATRASGYSR HSSRVAASNH
HSVAGYTHRG NGCAAATTGC GCATCACTCA ATCTAGGCTT ACCTTTGTCG

FIG. 4D-1

CCATATTCAA AGCGCCATTC ATTGGGGCGT ATTTCACTAT GTTGTGACAA
TAAAGCGCGC AAAHGNAAAS SRARGRYSGY YSASGYTYRG HARGTRGASN
RARGGSRHSG NSRAAARGAA TAGCCTCTTA CCATTAAACC TTGAGTTTTA
GCTTCTTGTT TAATGTAGCG ATTAACCTTA ATTAACTCAT CTTCAGGCAG
CCATGACTTA ACCAACTCTY RGYARGVAMT GYGNTHRYSA AGGNYSTYRA
RGASNVAYSG ASGRTRSRYS VAGTGTAGTC TGGTTATCGC ACTCTTGTAT
TGTTAACGGA CAGAAGTATA AGGAAATCAA
*
9157

FIG. 4D-2

9681
*
MSMFLNSKLS RSVKLAISAG LTASLAMPVF AEETAAEEQI ERVAVTGSRI
AKAELTQPAP VVSLSAEELT KFGNQDLGSV LAELPAIGAT NTIIGNNNSN
SSAGVSSADL RRLGANRTLV LVNGKRYVAG QPGSAEVDLS TIPTSMISRV
EIVTGGASAI YGSDAVSGVI NVILKEDFEG FEFNARTSGS TESVGTQEHS
FDILGGANVA DGRGNVTFYA GYERTKEVMA TDIRQFDAWG TIKNEADGGE
DDGIPDRLRV PRVYSEMINA TGVINAFGGG IGRSTFDSNG NPIAQQERDG
TNSFAFGSFP NGCDTCFNTE AYENYIPGVE RINVGSSFNF DFTDNIQFYT
DFRYVKSDIQ QQFQPSFRFG NININVEDNA FLNDDLRQQM LDAGQTNASF
AKFFDELGNR SAENKRELFR YVGGFKGGFD ISETIFDYDL YYVYGETNNR
RKTLNDLIPD NFVAAVDSVI DPDTGLAACR SQVASAQGDD YTDPASVNGS
DCVAYNPFGM GQASAEARDW VSADVTREDK ITQQVIGGTL GTDSEELFEL
QGGAIAMVVG FEYREETSGS TTDEFTKAGF LTSAATPDSY GEYDVTEYFV
EVNIPVLKEL PFAHELSFDG AYRNADYSHA GKTEAWKAGM FYSPLEQLAL
RGTVGEAVRA PNIAEAFSPR SPGFGRVSDP CDADNINDDP DRVSNCAALG
IPPGFQANDN VSVDTLSGGN PDLKPETSTS FTGGLVWTPT FADNLSFTVD
YYDIQIEDAI LSVATQTVAD NCVDSTGGPD TDFCSQVDRN PTTYDIELVR
SGYLNAAALN TKGIEFQAAY SLDLESFNAP GELRFNLLGN QLLELERLEF
QNRPDEINDE KGEVGDPELQ FRLGIDYRLD DLSVSWNTRY IDSVVTYDVS
ENGGSPEDLY PGHIGSMTTH DLSATYYINE NFMINGGVRN LFDALPPGYT
NDALYDLVGR RAFLGIKVMM
*
12590

FIG. 4E

13040

MAKINSEHLD EATITSNKCT QTETEARHRN ATTTPEMRRF IQESDLSVSQ
LSKILNISEA TVRKWRKRDS VENCPNTPHH LNTTLTPLQE YVVVGLRYQL
KMPLDRLLKA TQEFINPNVS RSGLARCLKR YGVSRVSDIQ SPHVPMRYFN
QIPVTQGSDV QTYTLHYETL AKTLALPSTD GDNVVQVVSL TIPPKLTEEA
PSSILLGIDP HSDWIYLDIY QDGNTQATNR YMAYVLKHGP FHLRKLLVRN
YHTFLQRFPG ATQNRRPSKD MPETINKTPE TQAPSGDS

13903

FIG. 4F

13906
*
MSQTSKPTNS ATEQAQDSQA DSRLNKRLKD MPIAIVGMAS IFANSRYLNK
FWDLISEKID AITELPSTHW QPEEYYDADK TAADKSYCKR GGFLPDVDFN
PMEFGLPPNI LELTDSSQLL SLIVAKEVLA DANLPENYDR DKIGITLGVG
GGQKISHSLT ARLQYPVLKK VFANSGISDT DSEMLIKKFQ DQYVHWEENS
FPGSLGNVIA GRIANRFDFG GMNCVVDAAC AGSLAAMRMA LTELTEGRSE
MMITGGVCTD NSPSMYMSFS KTPAFTTNET IQPFDIDSKG MMIGEGIGMV
ALKRLEDAER DGDRIYSVIK GVGASSDGKF KSIYAPRPSG QAKALNRAYD
DAGFAPHTLG LIEAHGTGTA AGDAAEFAGL CSVFAEGNDT KQHIALGSVK
SQIGHTKSTA GTAGLIKAAL ALHHKVLPPT INVSQPSPKL DIENSPFYLN
TETRPWLPRV DGTPRRAGIS SFGFGGTNFH FVLEEYNQEH SRTDSEKAKY
RQRQVAQSFL VSASDKASLI NELNVLAASA SQAEFILKDA AANYGVRELD
KNAPRIGLVA NTAEELAGLI KQALAKLAAS DDNAWQLPGG TSYRAAAVEG
KVAALFAGQG SQYLNMGRDL TCYYPEMRQQ FVTADKVFAA NDKTPLSQTL
YPKPVFNKDE LKAQEAILTN TANAQSAIGA ISMGQYDLFT AAGFNADMVA
GHSFGELSAL CAAGVISADD YYKLAFARGE AMATKAPAKD GVEADAGAMF
AIITKSAADL ETVEATIAKF DGVKVANYNA PTQSVIAGPT ATTADAAKAL
TELGYKAINL PVSGAFHTEL VGHAQAPFAK AIDAAKFTKT SRALYSNATG
GLYESTAAKI KASFKKHMLQ SVRFTSQLEA MYNDGARVFV EFGPKNILQK
LVQGTLVNTE NEVCTISINP NPKVDSDLQL KQAAMQLAVT GVVLSEIDPY
QADIAAPAKK SPMSISLNAA NHISKATRAK MAKSLETGIV TSQIEHVIEE
KIVEVEKLVE VEKIVEKVVE VEKVVEVEAP VNSVQANAIQ TRSVVAPVIE
NQVVSKNSKP AVQSISGDAL SNFFAAQQQT AQLHQQFLAI PQQYGETFTT
LMTEQAKLAS SGVAIPESLQ RSMEQFHQLQ AQTLQSHTQF LEMQAGSNIA
ALNLLNSSQA TYAPAIHNEA IQSQVVQSQT AVQPVISTQV NHVSEQPTQA
PAPKAQPAPV TTAVQTAPAQ VVRQAAPVQA AIEPINTSVA TTTPSAFSAE

FIG. 4G-1

TALSATKVQA TMLEVVAEKT GYPTEMLELE MDMEADLGID SIKRVEILGT
VQDELPGLPE LSPEDLAECR TLGEIVDYMG SKLPAEGSMN SQLSTGSAAA
TPAANGLSAE KVQATMMSVV AEKTGYPTEM LELEMDMEAD LGIDSIKRVE
ILGTVQDELP GLPELSPEDL AECRTLGEIV DYMNSKLADG SKLPAEGSMN
SQLSTSAAAA TPAANGLSAE KVQATMMSVV AEKTGYPTEM LELEMDMEAD
LGIDSIKRVE ILGTVQDELP GLPELNPEDL AECRTLGEIV TYMNSKLADG
SKLPAEGSMH YQLSTSTAAA TPVANGLSAE KVQATMMSVV ADKTGYPTEM
LELEMDMEAD LGIDSIKRVE ILGTVQDELP GLPELNPEDL AECRTLGEIV
DYMGSKLPAE GSANTSAAAS LNVSAVAAPQ AAATPVSNGL SAEKVQSTMM
SVVAEKTGYP TEMLELGMDM EADLGIDSIK RVEILGTVQD ELPGLPELNP
EDLAECRTLG EIVDYMNSKL ADGSKLPAEG SANTSATAAT PAVNGLSADK
VQATMMSVVA EKTGYPTEML ELGMDMEADL GIDSIKRVEI LGTVQDELPG
LPELNPEDLA ECRTLGEIVS YMNSQLADGS KLSTSAAEGS ADTSAANAAK
PAAISAEPSV ELPPHSEVAL KKLNAANKLE NCFAADASVV INDDGHNAGV
LAEKLIKQGL KVAVVRLPKG QPQSPLSSDV ASFELASSQE SELEASITAV
IAQIETQVGA IGGFIHLQPE ANTEEQTAVN LDAQSFTHVS NAFLWAKLLQ
PKLVAGADAR RCFVTVSRID GGFGYLNTDA LKDAELNQAA LAGLTKTLSH
EWPQVFCRAL DIATDVDATH LADAITSELF DSQAQLPEVG LSLIDGKVNR
VTLVAAEAAD KTAKAELNST DKILVTGGAK GVTFECALAL ASRSQSHFIL
AGRSELQALP SWAEGKQTSE LKSAAIAHII STGQKPTPKQ VEAAVWPVQS
SIEINAALAA FNKVGASAEY VSMDVTDSAA ITAALNGRSN EITGLIHGAG
VLADKHIQDK TLAELAKVYG TKVNGLKALL AALEPSKIKL LAMFSSAAGF
YGNIGQSDYA MSNDILNKAA LQFTARNPQA KVMSFNWGPW DGGMVNPALK

FIG. 4G-2

KMFTERGVYV IPLKAGAELF ATQLLAETGV QLLIGTSMQG GSDTKATETA
SVKKLNAGEV LSASHPRAGA QKTPLQAVTA TRLLTPSAMV FIEDHRIGGN
SVLPTVCAID WMREAASDML GAQVKVLDYK LLKGIVFETD EPQELTLELT
PDDSDEATLQ ALISCNGRPQ YKATLISDNA DIKQLNKQFD LSAKAITTAK
ELYSNGTLFH GPRLQGIQSV VQFDDQGLIA KVALPKVELS DCGEFLPQTH
MGGSQPFAED LLLQAMLVWA RLKTGSASLP SSIGEFTSYQ PMAFGETGTI
ELEVIKHNKR SLEANVALYR DNGELSAMFK SAKITISKSL NSAFLPAVLA
NDSEAN
*
22173

FIG. 4G-3

22203

*MPLRIALILL PTPQFEVNSV DQSVLASYQT LQPELNALLN SAPTPEMLSI
TISDDSDANS FESQLNAATN AINNGYIVKL ATATHALLML PALKAAQMRI
HPHAQLAAMQ QAKSTPMSQV SGELKLGANA LSLAQTNALS HALSQAKRNL
TDVSVNECFE NLKSEQQFTE VYSLIQQLAS RTHVRKEVNQ GVELGPKQAK
SHYWFSEFHQ NRVAAINFIN GQQATSYVLT QGSGLLAAKS MLNQQRLMFI
LPGNSQQQIT ASITQLMQQL ERLQVTEVNE LSLECQLELL SIMYDNLVNA
DKLTTRDSKP AYQAVIQASS VSAAKQELSA LNDALTALFA EQTNATSTNK
GLIQYKTPAG SYLTLTPLGS NNDNAQAGLA FVYPGVGTVY ADMLNELHQY
FPALYAKLER EGDLKAMLQA EDIYHLDPKH AAQMSLGDLA IAGVGSSYLL
TQLLTDEFNI KPNFALGYSM GEASMWASLG VWQNPHALIS KTQTDPLFTS
AISGKLTAVR QAWQLDDTAA EIQWNSFVVR SEAAPIEALL KDYPHAYLAI
IQGDTCVIAG CEIQCKALLA ALGKRGIAAN RVTAMHTQPA MQEHQNVMDF
YLQPLKAELP SEISFISAAD LTAKQTVSEQ ALSSQVVAQS IADTFCQTLD
FTALVHHAQH QGAKLFVEIG ADRQNCTLID KIVKQDGASS VQHQPCCTVP
MNAKGSQDIT SVIKALGQLI SHQVPLSVQP FIDGLKRELT LCQLTSQQLA
AHANVDSKFE SNQDHLLQGE V*

24515

FIG. 4H

24518

*MSLPDNASNH LSANQKGASQ ASKTSKQSKI AIVGLATLYP DAKTPQEFWQ
NLLDKRDSRS TLTNEKLGAN SQDYQGVQGQ SDRFYCNKGG YIENFSFNAA
GYKLPEQSLN GLDDSFLWAL DTSRNALIDA GIDINGADLS RAGVVMGALS
FPTTRSNDLF LPIYHSAVEK ALQDKLGVKA FKLSPTNAHT ARAANESSLN
AANGAIAHNS SKVVADALGL GGAQLSLDAA CASSVYSLKL ACDYLSTGKA
DIMLAGAVSG ADPFFINMGF SIFHAYPDHG ISVPFDASSK GLFAGEGAGV
LVLKRLEDAE RDNDKIYAVV SGVGLSNDGK GQFVLSPNPK GQVKAFERAY
AASDIEPKDI EVIECHATGT PLGDKIELTS METFFEDKLQ GTDAPLIGSA
KSNLGHLLTA AHAGIMKMIF AMKEGYLPPS INISDAIASP KKLFGKPTLP
SMVQGWPDKP SNNHFGVRTR HAGVSVFGFG GCNAHLLLES YNGKGTVKAE
ATQVPRQAEP LKVVGLASHF GPLSSINALN NAVTQDGNGF IELPKKRWKG
LEKHSELLAE FGLASAPKGA YVDNFELDFL RFKLPPNEDD RLISQQLMLM
RVTDEAIRDA KLEPGQKVAV LVAMETELEL HQFRGRVNLH TQLAQSLAAM
GVSLSTDEYQ ALEAIAMDSV LDAAKLNQYT SFIGNIMASR VASLWDFNGP
AFTISAAEQS VSRCIDVAQN LIMEDNLDAV VIAAVDLSGS FEQVILKNAI
APVAIEPNLE ASLNPTSASW NVGEGAGAVV LVKNEATSGC SYGQIDALGF
AKTAETALAT DKLLSQTATD FNKVKVIETM AAPASQIQLA PIVSSQVTHT
AAEQRVGHCF AAAGMASLLH GLLNLNTVAQ TNKANCALIN NISENQLSQL
LISQTASEQQ ALTARLSNEL KSDAKHQLVK QVTLGGRDIY QHIVDTPLAS
LESITQKLAQ ATASTVVNQV KPIKAAGSVE MANSFETESS AEPQITIAAQ
QTANIGVTAQ ATKRELGTPP MTTNTIANTA NNLDKTLETV AGNTVASKVG
SGDIVNFQQN QQLAQQAHLA FLESRSAGMK VADALLKQQL AQVTGQTIDN
QALDTQAVDT QTSENVAIAA ESPVQVTTPV QVTTPVQISV VELKPDHANV
PPYTPPVPAL KPCIWNYADL VEYAEGDIAK VFGSDYAIID SYSRRVRLPT
TDYLLVSRVT KLDATINQFK PCSMTTEYDI PVDAPYLVDG QIPWAVAVES
GQCDLMLISY LGIDFENKGE RVYRLLDCTL TFLGDLPRGG DTLRYDIKIN
NYARNGDTLL FFFSYECFVG DKMILKMDGG CAGFFTDEEL ADGKGVIRTE

FIG. 4I-1

EEIKARSLVQ KQRFNPLLDC PKTQFSYGDI HKLLTADIEG CFGPSHSGVH
QPSLCFASEK FLMIEQVSKV DRTGGTWGLG LIEGHKQLEA DHWYFPCHFK
GDQVMAGSLM AEGCGQLLQF YMLHLGMHTQ TKNGRFQPLE NASQQVRCRG
QVLPQSGVLT YRMEVTEIGF SPRPYAKANI DILLNGKAVV DFQNLGVMIK
EEDECTRYPL LTESTTASTA QVNAQTSAKK VYKPASVNAP LMAQIPDLTK
EPNKGVIPIS HVEAPITPDY PNRVPDTVPF TPYHMFEFAT GNIENCFGPE
FSIYRGMIPP RTPCGDLQVT TRVIEVNGKR GDFKKPSSCI AEYEVPADAW
YFDKNSHGAV MPYSILMEIS LQPNGFISGY MGTTLGFPGL ELFFRNLDGS
GELLREVDLR GKTIRNDSRL LSTVMAGTNI IQSFSFELST DGEPFYRGTA
VFGYFKGDAL KDQLGLDNGK VTQPWHVANG VAASTKVNLL DKSCRHFNAP
ANQPHYRLAG GQLNFIDSVE IVDNGGTEGL GYLYAERTID PSDWFFQFHF
HQDPVMPGSL GVEAIIETMQ AYAISKDLGA DFKNPKFGQI LSNIKWKYRG
QINPLNKQMS MDVSITSIKD EDGKKVITGN ASLSKDGLRI YEVFDIAISI
EESV

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30529

FIG. 4I-2

30730

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*
MNPTATNEML SPWPWAVTES NISFDVQVME QQLKDFSRAC
YVVNHADHGF GIAQTADIVT EQAANSTDLP VSAFTPALGT
ESLGDNNFRR VHGVKYAYYA GAMANGISSE ELVIALGQAG
ILCGSFGAAG LIPSRVEAAI NRIQAALPNG PYMFNLIHSP
SEPALERGSV ELFLKHKVRT VEASAFLGLT PQIVYYRAAG
LSRDAQGKVV VGNKVIAKVS RTEVAEKFMM PAPAKMLQKL
VDDGSITAEQ MELAQLVPMA DDITAEADSG GHTDNRPLVT
LLPTILALKE EIQAKYQYDT PIRVGCGGGV GTPDAALATF
NMGAAYIVTG SINQACVEAG ASDHTRKLLA TTEMADVTMA
PAADMFEMGV KLQVVKRGTL FPMRANKLYE IYTRYDSIEA
IPLDEREKLE KQVFRSSLDE IWAGTVAHFN ERDPKQIERA
EGNPKRKMAL IFRWYLGLSS RWSNSGEVGR EMDYQIWAGP
ALGAFNQWAK GSYLDNYQDR NAVDLAKHLM YGAAYLNRIN
SLTAQGVKVP AQLLRWKPNQ RMA
                        *
                      32358
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FIG. 4J

32834

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MRKPLQTINY DYAVWDRTYS YMKSNSASAK RYYEKHEYPD

DTFKSLKVDG VFIFNRTNQP VFSKGFNHRN DIPLVFELTD

FKQHPQNIAL SPQTKQAHPP ASKPLDSPDD VPSTHGVIAT

RYGPAIYYSS TSILKSDRSG SQLGYLVFIR LIDEWFIAEL

SQYTAAGVEI AMADAADAQL ARLGANTKLN KVTATSERLI

TNVDGKPLLK LVLYHTNNQP PPMLDYSIII LLVEMSFLLI

LAYFLYSYFL VRPVRKLASD IKKMDKSREI KKLRYHYPIT

ELVKVATHFN ALMGTIQEQT KQLNEQVFID KLTNIPNRRA

FEQRLETYCQ LLARQQIGFT LIIADVDHFK EYNDTLGHLA

GDEALIKVAQ TLSQQFYRAE DICARFGGEE FIMLFRDIPD

EPLQRKLDAM LHSFAELNLP HPNSSTANYV TVSLGVCTVV

AVDDFEFKSE SHIIGSQAAL IADKALYHAK ACGRNQALSK

TTITVDEIEQ LEANKIGHQ

*

34327

FIG. 4K

1

AATAGATCGACTCGCAAAAGTTGCTTAAGATAGTGTCAATATAGCTTCTTATTTGTA
AATATTGTTTTTTATGTGTAAACATGTTTAGTGTGTGTAAATGCTGTTAATTATCCT
TTTGGGATTGTAATAGCTGATGTTGCTGGCTAATGAGTACTTTTAGTTCGGCAATAT
CTTGCTTTAAATCGCTAACTTCAGTTTTTAATTCACCCACACTTGTTGTATTTTTAA
GGCTCTCTTCCCCACCATCGACAAACCAGGATGATATGAAACCGGTAAACGTACCAA
AGAGACCGACACCTGCAGTCATGAGTAATGCCGCAATGATACGTCCGCCAGTGGTGA
CGGGGTAGTAGTCACCGTAACCAACAGTCGTTATTGTCACAAATGACCACCAAAGTG
CGTCGATGCCGTTATTGATGTTACTGCCTACTTGATCCTGTTCTAACAATAAAATAC
CGATAGCACCAAAGGTGACAAGGATGAAGGATATCGCAGATACCAGCGAAAAGGTGG
CTTTAAACCGATGTTCAAAAATCATTTTTAAGATAATTTTTGATGAGCGTATATTCT
GAATAGATCTTAATACTCTAGCGATACGAATTATGCGAATAAACTGCAGTTGCTCGA
CCATCGGAATACTCGACAGTAGGTCAATCCAACCCCATTTCATAAACTGAAATTTAT
TCTCAGCTTGGTGAAAGCGAATTACAAAGTCAGTGAAAAAGAATAAGCAAATCGTAT
TATCTACGCTCGTTAATATTTCAGTGACGTTACTTGAAAAGGTAAAAATAAGTTGCA
GTAGTGATGATACGACCACATGAAGTGATAAAATAAGCATGAAAATCTGAAATGGAT
TTACATCACTGTTGTTTTTGGTGCCACTTTTAAGGTTCGTTTTCACAATCTGCTGCC
TCGGTTCATTGATTTTGTTAATATAAACCTTAGTCAGTAGCAAGACAAAATATATTT
ACATCAATGTCATCGTATTATTCAACCGCGCGTCGTGTATTCAGACCAAGATCGTTG
TATATGTTAGTCATGTAGCGATGAGATTATCATGCGACAGGAGAGAATTATGTTTGT
TATTATTTTTTACGTACCTAAAGTTAATGTTGAAGAAGTAAAACAGGCGTTATTTAA
CGTCGGAGCTGGCACCATCGGTGATTATGATAGTTGTGCTTGGCAATGTTTGGGGAC
TGGGCAGTTCCAACCTTTACTTGGTAGCCAGCCACATATTGGTAAGCTAAATGAGGT
TGAATTCGTTGATGAGTTTAGAGTAGAAATGGTTTGTCGAGCAGAAAATGTAAGGGC
AGCAATAAATGCACTTATTGCTGCGCACCCTTATGAAGAACCTGCTTATCATATTCT
GCAAACATTGAATCTTGATGAGTTACCTTAAGTTAGATGCACTGCACTTAATTGGTT
CGCTGTGCTAGGTTAGCAATTAGCAATTTTGACCATGTTAGCGATAGTTTTGGCACA

FIG. 5-1

AGTGATCGATATTAAACTATCCGATTCAGATCCCATTTTTACTGCTGAATTAGGTTT
CATTACACTTGTTCTAGTGGTTTTTCCCGACAGGTGTAACTCTGTTACTTGCGTAAG
GTTGATAATCTCTACCGCATTGGCAGGAGTTACACCTGCACCAGGCATAATACTAAT
TCTACCATCTGCTTGGTTAACTAACGTTTGGATTAAGGCGCAGCCTTCTAGCGCTTG
AGCTTGTTGACCAGAGGTTAAAATACGCTCACAACCAGCAGTGATCAAGGTCTCCAA
GGCTTGTTGTGGATCATTACACAAGTCGAAAGCGCGGTGGAAGGTTACGCCGAGATC
ACGTGATGCCACCATTAAGCGTTTTAAAGCTGGCTCGTCAATATTACCATCTGCTGT
TAACGCGCCAATAACGACCCCTTGGACACCGAGTAACTTCATGAATTTGATGTCGGA
AACCATAATATCAACTTCTTGTTCGCTATATACAAAATCACCGGCGCGAGGGCGAAT
AATGGCATAAATGGGGATCGTTGCTAGATCAATAGACTTTTGTACAAAACCTGCGTT
GGCGGTCAAGCCACCTAATGCTAATGCCGAGCACAACTCAATACGATCGGCGCCAGA
TGCTTGAGCCGTCAGCAGTGATTCTATATTATCGACACATACTTCTATTGTCATTGT
CATATACTTCTCTTTAAAAAGTTTATTAAAAATAATAAAGCCAGCATAAGTCGTTTT
ATACAATATGAAAGGGGAAAAGGCGACTTAGCTCGCCTAGATCAATTATTATGGCAG
AATACTGCCGTATTGTGATTAGAAAGACAGTTTTTTAAGCTCAATAGCCGTTATCGC
GTTGTTATCTACCATCGTGTAACTTTTCTGGCCTGGGTGCTTTATTAACACTGTTTC
AGTGGCTGGATTAGGGTGAAATGATTCTTTTTTCAAATCTGTTTTTTTGTATTTGAA
CGTACCTGTAATGTCTTGCTGCTCACGAAGACGTACAAATATTGGTTGCGCATAGCT
TGGTAGTGCCGCATTGACATGTTGATAGAATTCAGACGCTGAAAATTCATGAATAGG
GCAATTCAAAGTCAGCGCGACCATGCCTGCTCGGCCATCGTGATGTGGGAGCTTGAC
ACCATAAGCCACACTTTGCTCAATTTGCACAAAATCGTTAACTTGAGCTTCTACTTG
CGTCGTGGCGACATTTTCACCTTTCCAGCGGAATGTATCACCTAATCTATCCACAAA
GGAAATATGGCGATAACCTTGGTAATGAACGAGATCGCCGGTATTAAAATAACAGTC
ACCGTCTTTTAATACTGACTTAAATAGCTTTTTATTACTTTCGTTGTCATCGGTATA
ACCATCAAATGGTGAACGTTTAGTTATCTTTGTTAGCAGTAGCCCTGTTTCTCCCGT

FIG. 5-2

TTTTACTTTGGTCATTTTCCCTTTCGCATTATACACAGGTTTGTCATTGTCAATATC
ATATTGTATGACGGTAAAAGCAAGTGGAGTAACCCCCGCTGTATGCGGTAAGTTCAG
CGCATTGGAGAACACAAGATTACACTCACTGGCGCCATAGAATTCATTAATATGCTC
GATCCCAAAACGTTGTTGGAAATGATCCCAAATTTCGGGGCGTAATCCATTACCTAT
GATTTTCTTTATATTATGCTGTTTGTCTTTATTGCTAGGCGGTACATTTAATAAATA
ACGGCAGAGCTCGCCGATGTAAGTAAACGCAGTGGCATTATGAGCACGAACTTCATC
CCAAAAGCGACTTGAACTGAATTTTTCAGAAAGTGCGAGGGTTGCTGCGCTACCAAA
CACGGCGCTTAATGACACTGTCAGTGCATTGTTATGGTATAGGGGGAGTGATAAATA
CAATACATCATCAGCTGTTAAGCGTAATGATGCCATCCCCATGCCTGCCATGGATTT
AAACCAACGGTGATGGCTCATTCTTGCTGCTTTTGGCAGTCCAGTTTTTCCCGAGGT
AAAGATATAAAACGCGCAATGCTTAAGCTGTATTTGTGCTGTTGATTCAGGGTTCAA
TACTGAATATCCTGCGACTAGTGTAGATATGTTTTTATAACCATCACTCATGTCTGG
CGTTTCTAAAGCGGGTACGTAAAAGACATTCTGTTGTAATGTCGATGACAAATTGGT
TTCAATATTATTAATGGCGGATGTGTATAGTTCATCTGCGATGAGTAATTTGGTATC
GACCACGCTAAGACTATGTTCGAGGATTGAATCCCGTTGTGTCGTATTTATCATACA
AGCAATCGCGCCAAGCTTGACAACTGCGAGGGCAATAATGATGGTTTCAGGCCTGTT
ATCGAGCATGATGGCGACTTTATCATTTTTACCAATGCCGTATTCATGAAGGAAATG
GGCATATTGATTTGCTTGCTTATTCAATGAATCGTAACTATAACGCTGGTCTTTAAA
TTGTATTGCGATCAAGTCAGAGTTATTGACAGCTTGCTGCTCTAGTAATAAACCAAT
AGACATAAAACGTTCGGGCTTTGCTTGTTGTAAGTGCCATAAGCCTTTGATGATTGG
CTTTGGGGTTTTTAATAGATTGATGGTACTTTTCAGGAATTGTTTGCCGGTTATAAC
AGTCATAAGCTAATTCTTTTTATCAAGAAGAGGGGTTATGACACCAAATAAATGGGT
CACGCGTTGGTTTAATTTGGTTAGACTAAATGTGTTGTTTTGCTGTGATAATGCGAC
GTTCAAACAAACTTGAGAAGGTAAAAAAATAGCATTTTTAAATTGAACATCAATACT
AATGTGTTGAATATCAATCAAGTTTTCTAACTGTGCGAGCACGCGTGCTTTAGCAAA

FIG. 5-3

CATGCCATGTGCTATTGCTGTTTTAAACCCCATTAGTTTCGCTGGGATAAAATGTAA
ATGGATTGGATTTGTGTCTTTGGAGATATAAGCATATTTATATACGTCAAAAGGACT
AAATTTAAACAATGAAATCGGCTCGTAAGCATAATTCGCTGGCGTATTTACTATTTT
CTCACCGCTGGAACGTTGAGATCGTTGGCACGTTTTTCGCTGTTTCGTTTTCTGTAA
GAATGTCGATGTACACTCCCACGCAAATTGTCCATCTACAAACACATCAATATGAGT
ATCAATGAAACGTCCTGTATCCGTTATGTACTCCTTAATTACACGACATGTGCTCGT
CAATATCGCGTTTAATGCTATCGGTTGATGTTGTGTTATGCGATTTCGATAATGGAC
TAGTCCTAATATAGATATCGGAAATTGTGTTGATGTCATGAGTTTCATCAATAATGG
AAAGATCATCACAAATGGATAAGTAACCGGTACATAGTTTGTGTTATTAAACCCACA
GCATTTAATATATTGCTTTAAATTTCGCTGATCTATTTTTTGTCCACTGATACTAAA
TTGCTCAGTACACACTTGTGTCGACCAAGTGTTCATCAGTGTTTTAACAATTGTATT
GACCACTGCTTTCACATATAAAAGCGAGATAATCGGTTGCTTTGTTAACAGTGTGAT
CTGGTTAGCGTGCATTGAAATAATTCATATAAGAGTATGTAGCATTTATGTTAATAT
TTTGTTTTGGAAGTTGAATTGGCGAATCCGTAATCGGTTTATGGCAGTTCGGTCAAA
TACTTCAGGTAAACTCGTTACTCATACCATTGATAGTGTTAAAGTGATTGACTGAAT
AAAGAATAGAGCTAAAAGTGGAAAAATTATGCAAGATGCGGGTATGTTATTACGCAT
TGCTTATGAGGCAATGAAAGAGTTAGAGGTTGATGTCATTGAAGTACTTTCTCGTTG
TAACATAAGTGAAGAAGTACTGAATGATAAGGATCTTCGCACACCTAATCATGCACA
AACACATTTTTGGCAAGTATTAGAAGACATATCACAAGATCCTAACATCGGCATTTC
ACTTGGTGAGAGAATGCCAGTGTTCACGGGGCAGGTATTACAGTATCTTTTTCTCAG
TAGTCCTACATTTGGTACTGGCTGGGAACGCGCAACAAAATACTTTCGATTAATCAG
TGATGCGGCGAGTGTTTCTATCAAGATGGAAGGCTGTGAAGCGCGATTATCTGTGAA
CTTAGATGGTTTAGCGGAAGATGCGAATCGTCATTTGAATGATTGCCTAGTGATCGG
TGCATTTAAATTTTGTTTATATGTGACAGAAGGCGAATTTAAAGTAAGCAAAATAGC
CTTTGCTCATGCTCGCCCGAAAGATATTACTGCCTATACCAATGTATTTACATGTCC

FIG. 5-4

GATTGAGTTTGCTGCCGAAGATAATTATATTTATTTCGATGCTGATTTACTCGAACG
TCCTTCTTCGCATGCGGAGCCTGAGCTATTCGCCTTACACGATCAGCTTGCAAGCCG
TAAAATAGCCAAGTTAGAACTGCAAGATTTAGTGGATAAAGTACGTAAGGTTATTGC
ACAACAACTTGAGTCTGGTGTGGTGACTTTAGAAAGTATCGCCACTGAACTTGACAT
GAAACCACGTATGCTAAGAGCGAAGTTAGCTGACATTGATTATAACTTTAATCAAAT
ACTCGCTGATTTTCGTTGCGAGTTATCAAAAAAACTGTTGGCGAATACGGACGAGTC
TATTGATCAGATTGTCTATCTCACTGGTTTTTCTGAACCAAGTACTTTTTATCGTGC
CTTTAAGCGCTGGGTTAAAATGACGCCAATTGAATATCGCCGTAGCAAACTCGCGGT
TAGGCATGCTAATCAACACGAGTCCTAAAAATTCGCTGCTTAGTGCATAGTGCATAG
TGCATAGTGCTAGTAAGCCAAGTACAAAGCGTTAAAGTTAAGTACTTGAGCGAACCA
TCAGACACCACTTACTAGATTAAGCACCTATTAATGATTGACCACAAATTCTGATCG
TATTGCCTGTGATCCCTGCAGCTTGAGGTTGCGCAAAAAAAGCTATCGCTTCAGCAA
CATCAACTGGCTTACCACCTTGTTTTAATGAATTCATACGACGACCAGCTTCACGAA
CTGTAAATGGAATCGCTGCTGTCATTTTTGTTTCAATAAAGCCTGGTGCAACAGCAT
TAATGGTGATGTATTTGTCTGCAAGCGGAGTTTGCATTGCATCAACATAACCAATGA
CTGCGGCCTTAGACGTTGCATAATTAGTCTGACCAAAGTTACCCGCAATCCCACTCA
TCGAAGACACACAAACAATGCGGCCATAGTCGTTGAGCAGATCATCATTTAGCAGTC
GCTCATTGATTCTTTCCATTGCCGACAAGTTAATATCCATCAGTACATCCCAATGGT
TATCCGGCATACGTGCTAGCGTTTTGTCTTTTGTTACCCCGGCATTATGGACGATGA
TATCAAGCGACTGTTCTCGCACAAAGTCAGCAATGATATTTGGGGCGTCAGCAGCGG
TAATATCAGCAACAATGCTGCTACCTTTCAAGCAATGAGCTACTTTTTCAAGGTCCT
GTTTTAATGCCGGAATGTCTAAGCAAATAACATGTGCGCCATCACGGGCGAGTGTTT
CAGCAATAGCAGCCCCGATGCCACGTGATGCACCAGTGACAAGTGCTGTCTTTCCTT
GTAATGGTTTTGCCGTGTTACTTGTTTCGTTAATAACTTCGTTAATAACTTCGTTAA

FIG. 5-5

TAACTTCGTTAATAGCCCCATTAATCGAACCGGGTTTTACGTTAATAACCTGTGCTG
AGATATAGGCTGATTTTGCTGAGGTTAAGAAACGTAGCGGGGCCTCTAATAATTGCT
CACTACCAGGTTGTACATAGATAAGTTGACAGGTACTACCATTCTTGCCTATTTCTT
TGGCGACACTGCGACAAAACCCTTCTAAAGATCTTTGTACAGTCGCGTAGCTTACAT
CGTCAAGATGTTCACTCGGATGACCTAACACGATCACTCTGCTGCATGGCGAGAGCT
GCTTAATTACAGGTTGAAAAAAACGATGTAATGCACTTAATTGCTTGCTGTTCTTAA
TGCCTGAGGCGTCGAAGATAATACCGTTGAAGCGATCTGTTTTAGCGATAGCATTAA
GGCTAATAGGTGTCGCGACTAAAGACGTTTGATTAAATTCAATATTAAGATCGGCTA
ACGCTGACGTGTTATTAGGATAAGAAATCGTGACTTCAGCATCTTTAAATGTGTTAA
GAATGGGTTTAATTAATTTGCTGTTGCTGGCTGCGCCGATGAGTAAGTTGCCAGAGA
TGAGATCGGTTCCCTGATCGTAGCGTGTTAACGTAACCGGTCGTGGCAGATTAAGCG
CTTTAAATAAACCTGATGTCCACTTGCCATTAGCGAGTTTTGCGTATGTATCCGTCA
TTTTCTAATCCTTGTTATAGTGAACAGTTTGAATCTCGAAGATGTACATGTGTTAAA
AATTATCTGATAGCTATGACTTATCTGCCACTACGTAATAATAAATAGACCAGTTCA
TTACATCGTTAATCGATATAGTATAACTAAATACTAAGTAAATTATAATGATAAGAC
TGTTATCGTACTCGGATCAAACTCTGATCAGCAAATAATCAAATTAGAGTTTTTATT
TTAAACTTGTATCAACAATGTTACATTAATGTATCTTACGTCTAATGTGCTACGGGC
ATATTTAAGTCACTAAATTAAAGGAATAAACCATGACAGGTCAAACAATAAGAAGAG
TAGCAATTATCGGCGGTAACCGTATCCCGTTTGCACGTTCAAATACAGCGTATTCAA
AACTAAGTAACCAAGATATGCTGACGGAAACTATCCGTGGCTTGGTGGTTAAATATA
ACCTACGTGGTGAACAACTGGGGAAGTTGTTGCTGGTGCGGTAATTAAGCATTCTC
GTGATTTTAACTTAACACGTGAAGCCGTGCTAAGTGCAGGTCTTGCACCTGAAACGC
CTTGTTATGACATTCAACAAGCTTGTGGTACTGGTCTAGCTGCAGCTATCCAAGTAG
CAAACAAAATTGCGCTTGGTCAAATAGAAGCGGGTATTGCTGGTGGTTCTGATACGA

FIG. 5-6

CATCAGATGCACCGATTGCAGTCAGTGAAGGCATGCGTAGTGTATTACTTGAGCTTA
ATCGAGCTAAAACGGGTAAGCAACGTTTGAAAGCACTATCTCGTCTACGTCTAAAAC
ACTTTGCGCCACTAACGCCTGCAAATAAAGAGCCGCGTACCAAAATGGCGATGGGCG
ATCATTGTCAAGTAACAGCGAAAGAGTGGAATATCTCACGTGAAGCACAAGATGCAT
TGGCCTGCGCAAGTCATCAAAAATTAGCTGCAGCATATGAAGAAGGTTTCTTTGATA
CGTTAGTTTCACCTATGGCCGGCTTAACGAAAGATAACGTATTACGCGCAGATACAA
CAGTTGAGAAACTGGCTAAATTGAAACCTTGTTTTGATAAAGTAAACGGCACTATGA
CGGCGGGTAACAGTACTAACCTTACCGATGGAGCATCAGCTGTATTACTTGCAAGTG
AAGAATGGGCAGCGGCACATAACTTACCAGTACAAGCTTATCTAACATTTGGTGAAA
CGGCCGCTATCGACTTCGTTGATAAGAAAGAAGGTCTGTTAATGGCGCCTGCATACG
CAGTGCCAAAAATGTTGAAGCGTGCTGGCCTTACATTACAAGACTTCGATTACTATG
AAATACATGAAGCATTTGCTGCGCAGTTATTAGCAACGCTAGCAGCTTGGGAAGACG
AAAAATTCTGTAAAGAAAAACTGGGTCTAGATGCTGCGCTTGGTTCAATTGATATGA
CCAAGTTAAACGTGAAAGGGAGTAGCTTAGCCACGGGTCACCCATTTGCCGCAACTG
GTGGTCGTGTTGTCGCTACGCTAGCGCAATTACTTGATCAGAAAGGTTCAGGTCGTG
GTTTGATCTCGATTTGTGCTGCTGGTGGTCAAGGTATCACGGCAATTTTAGAGAAAT
AAACGCACTGTTTATTATCTATTGATTAAGCTGTCCTGAGATACTGGATATTTTTAA
ATAAAACGCCAATACTGCAGAGTATTGGCGTTTTTTTGTAATACCAATTCCTATATA
ACGGTGCATTTTAAACACTTAATTTCCGGCATTGGTATCATAAAAAAGCAGCACCGA
AGTGCTGCTTGATTGTAGATTAACCTATTAAAATAGAGAGGCTAGAATTAGTCTTCG
TATGCTTCATTATGTACGCCAGCTGCACGACCCGATGGATCAGCATTGTTTTGGAAA
CTTTCATCCCAAGCTAATGCTTCTACAGTTGAACAAGCAACGGATTTACCAAACGGT
ACGCATTTCGCTGCTGAATCACCTGGGAAGTGATCTTCAAAGATGGCACGATAGTAG
TAACCTTCTTTCGTATCTGGTGTGTTAATTGGGAACTTAAATGCTGCACTTGCTAAC
ATTTGATCAGTTACCGCTTCTTCAACGTGTACTTTAAGTTGGTCAATCCAAGAATAA

FIG. 5-7

CCAACACCATCAGAGAATTGTTCTTTTTGACGCCATACAATTTCTTCAGGTAGTAAA
TCTTCAAATGCTTCTCGAATGATGTTTTTCTCAATGCGGTCGCCCGTGATCATTTTT
AGTTCAGGGTTTAGACGCATTGACGCATCAACAAATTCTTTATCTAAGAAAGGAACA
CGTGCTTCGATGCCCCAAGCTGCCATAGATTTGTTTGCACGTAAGCAATCAAACATA
TGTAATTTATTTACTTTACGTACCGTCTCTTCATGGAATTCTTTCGCATTTGGCGCT
TTGTGGAAGTACAAGTAACCACCGAACAGTTCATCAGCACCTTCACCAGAAAGCACC
ATCTTAATCCCCATGGCTTTAATTTTACGTGCCATTAGGTACATAGGGGTTGATGCA
CGAATTGTTGTTACATCGTAGGTTTCAATGTGGTAAATCACGTCGCGTAAAGCGTCG
ATACCTTCTTGCACAGTAAATTCAATTGAATGATGGATAGTACCTAAGTGATCTGCC
ACTTTTTGTGCAGCGGCTAAATCTGGAGAACCATTTAGGCCTACAGAGAAAGAGTGT
AGTTGTGGCCACCATGCTTCGGTTTTACCACCGTCTTCAATACGACGTTTTGCATAC
TGTTGGGTGATTGCTGAAATAACAGATGAATCTAACCCGCCTGATAATAATACGCCG
TAAGGTACATCACACATTAATTGACGTTTAACTGCATCTTCCAAACCTTGCTTAACA
ACGCTTTTATCACCACCATTTTGTGCAACGTTATCAAAATCTTTCCAATCACGTTGA
TAATAAGGCGTGACTACACCATCCTTACTCCACAGGTAATGACCTGCTGGGAATTCT
TCAATTTGAGTACAAATTGGCACTAGTGCTTTCATTTCAGAGGCAACATAAAAGTTA
CCGTGTTCATCATAGCCCGTATAAAGAGGGATGATACCGATATGGTCACGGCCAATC
AGGTAAGCGTCCTCTGTTTCGTCATATAAAGCGAAAGCAAAAATACCATTTAGATCA
TCTAAAAATTGTGTGCCTTTTTCTTTATATAGCGCAAGTATCACTTCGCAATCTGAT
TCTGTTTGGAATTCAAAGTCTACGTTCAGCGTTTTCTTTAAATCTTTGTGGTTATAA
ATTTCACCATTAACAGCAAGTACGTGTGTCTTTTCTTCATTATATAGCGGCTGTGCA
CCATTATTTACATCGACAATAGCAAGACGTTCATGAACTAAAATAGCATTGTCACTT
GTATAGATACCTGACCAATCTGGGCCGCGGTGACGTAGTAACTTTGATAGTTCTAGT
GCTTGTTCGCGAAGAGGTTTAATGTCTGATTTGATGTCTAGAATTCCGAATATTGAG

FIG. 5-8

CACATAACTAATTCCTTCTGGGGCTGCGTCTGCAGCTAACTTTCTAAATAGTGTGTC
TAATTTGCCACATTGTAGATTTAATGCAAACATTAATGATAAAACATTTATAAAAAA
TGTAATTCAATGTGGAATCGATAATTTAATGGCTTAAAAGTGAAGATCCATTAATTG
TGATGGCGAGGTGATAGACCAATGTAGACCTTAATGAATAAAGCAGGCACGATTGAA
TCCATTCAACGCAAAGTGGTACTAACTATTGTTTTAAACGTTATAAATAGTGTTTTA
AAGGTTATAAGTAAATAATTTAAAAACAATAATAATCCACATGCATTAAATTTATCA
TGATAAACCGCTATATCTCAATGGCAATTTGGGATAAGTGTAAAATATATGTAAAAT
GAATGAGTTGACTTGCTTTTTTTACACTAAGTGATGAAATTAAAGCTAGATGTCGTT
GTTAGCATTGATTAATAACGTACTAAAATACGACATCTAGTATAGAAATTTAAAAAA
CAGTTGGTTTTGATAGCATAACTGCATAAACTAATCAGCTTATTGTCTGTAATATTT
TTGTAATTTAAATAGGTTTAATAAAATTATATGTCTGATAAATATAAACCGTACGAC
CTTTCCTTTAAAAAGACGTTTTTGCTGCCTAAGTTTTGGCCTGTGTGGTTCGGGGTG
TTTGCAATATACTTATTAGCTTTTATGCCAGTAAAGCCGCGTGATAAATTTGCTCGA
TTCATAGCGAAGAAATTGTTTAGTCTAAAAATGATGGCAAAGCGTAAAAAGGTAGCA
AAGATCAATTTATCTATGTGCTTCCCTGAAATGGATGATACGGAACAAGACCGTATA
ATCATGGTCAATCTAGTTACTTTTTGTCAAACTATCTTAAGTTATGCAGAGCCAAGT
GCGCGTAGTCGTGCTTATAACCGTGACCGTATGATAGTGCATGGTGGCGAGAATTTA
TTTCCGCTACTTGAACAAGGTAAGGCTTGTATCTTATTAGTGCCGCATAGCTTCGCT
ATTGATTTTGCAGGTTTACACATTGCTTCTTATGGCGCGCCATTTTGTACTATGTTT
AACAATTCTGAGAATGAGTTGTTCGATTGGCTGATGACACGTCAACGCGCTATGTTT
GGAGGCACTGTTTATCACCGCAAGGCAGGGCTAGGGGCTCTAGTTAAATCACTTAAG
AGCGGTGAAAGCTGTTATTACTTACCTGATGAAGACCATGGACCTAAGCGTAGTGTA
TTTGCGCCTTTATTTGCGACTCAAAAAGCAACTTTACCTGTAATGGGCAAGCTAGCA
GAAAAAACAAATGCACTCGTTGTTCCTGTTTATGCGGCATATAATGAATCACTAGGT
AAATTTGAAACCTTTATTCGACCAGCAATGCAAAACTTTCCATCAGAAAGCCCAGAA
CAAGATGCAGTGATGATGAATAAAGAGATTGAAGCCTTGATTGAATGTGGTGTTGAT

FIG. 5-9

CAATATATGTGGACACTTAGATTATTGAGAACACGTCCGGACGGTAAAAAAATCTAC
TAATAAAGTTTAATAAACACCATAATCTTCGTTGAATATGGTGTTTACCCCCCTGAA
TACCCTCTAAATTAATAACAAAAAAAGCCATTTACGTAACATCTAATGATGATTTAG
CCTGCACTTGCTTTGTTTTTAGTCTTAAGAGCCTAATAAACTTGATCTAGGTATAGA
TTCTGTCTTTCTTTACGTAACGCGATCTATTTTTTTAACCGATAGTTGTTATAATT
AGTTTCATATGAAAGAGATATCGTTTCAGTAAAAGCTATTTCGTTTCAATAGATAAT
TTATTTATAGTCATATTTTCTGTAATGACAATCATTTTCTCATCTAGACTATAGATA
AGAATACGAATTAAGTAAGAACATTAATTTTACAAGAATATAAAATATCCCATCGGA
GCTATAAGAATGAAAAAGACTAAAATTGTTTGTACAATTGGTCCAAAAACTGAATCA
GTAGAGAAACTAACAGAGCTTGTTAATGCAGGCATGAACGTTATGCGTTTAAATTTC
TCTCATGGTAACTTTGCTGAACATTCAGTGCGTATTCAAAATATCCGTCAAGTAAGT
GAAAACCTGAATAAGAAAATTGCTGTTTTACTGGATACTAAAGGTCCAGAAATCCGT
ACGATTAAACTAGAAAACGGTGACGATGTAATGTTGACCGCTGGTCAGTCATTCACG
TTTACAACAGACATTAACGTGGTAGGTAATAAAGACTGTGTTGCTGTAACATATGCT
GGTTTTGCTAAAGACCTTAATCCTGGTGCAATCATCCTTGTTGATGATGGTTTAATT
GAAATGGAAGTTGTTGCAACAACTGACACTGAAGTTAAATGTACAGTATTAAATACT
GGTGCACTTGGTGAAAATAAAGGCGTTAACTTACCTAACATCAGTGTAGGTCTACCT
GCATTGTCAGAAAAAGATAAAGCTGATTTAGCGTTTGGTTGTGAGCAAGAAGTTGAT
TTTGTTGCTGCATCATTTATTCGTAAGGCTGATGATGTAAGAGAAATTCGTGAAATC
CTATTTAATAATGGTGGCGAAAACATTCAGATTATCTCGAAAATTGAAAACCAAGAA
GGTGTAGACAATTTCGATGAAATCTTAGCTGAATCAGACGGTATCATGGTTGCTCGT
GGCGATCTCGGTGTTGAGATCCCAGTTGAAGAAGTGATCATGGCACAGAAGATGATG
ATCAAAAAATGTAATAAAGCAGGTAAAGTTGTAATTACTGCAACACAAATGCTTGAT
TCAATGATCAGTAACCCACGTCCAACACGTGCAGAAGCGGGCGATGTTGCCAATGCT
GTGCTTGACGGTACCGACGCGGTAATGCTTTCTGGTGAAACTGCGAAAGGTAAATAC

FIG. 5-10

CCAGTTGAAGCTGTGTCTATCATGGCAAACATCTGTGAACGTACTGATAACTCAATG
TCTTCGGATTTAGGTGCGAACATTGTTGCTAAAAGCATGCGCATTACAGAAGCTGTG
TGTAAAGGTGCGGTAGAAACAACAGAAAAATTGTGTGCTCCACTTATTGTTGTTGCA
ACTCGTGGCGGTAAATCAGCAAAATCTGTTCGTAAATACTTCCCGAAAGCAAATATT
CTTGCTATCACAACAAATGAAAAAGCAGCGCAACAGTTATGCCTAACTAAAGGCGTA
AGCAGCTGCATCGTTGAGCAGATTGATAGCACTGATGAGTTCTACCGTAAAGGTAAA
GAGCTTGCATTAGCAACTGGTTTAGCTAAAGAAGGCGATATCGTTGTTATGGTATCA
GGTGCGTTAGTACCATCAGGTACAACGAATACGGCATCTGTTCACCAACTTTAAGTT
GCCATATTGATATTATAAAAAAGAGAGCGTATGCTCTCTTTTTTTATATCTGTAGTT
TATATGTCTGTACAAAAAAATGATAAAGAGTACATAAACTATTAATATAGCGTAATA
TATAATGATTAACGGTGATGAAAGGGTTAAATAAATGGATAGTGCTAAACATAAAAT
TGGCTTAGTCCTTTCTGGCGGTGGTGCGAAAGGTATTGCTCATCTTGGTGTATTAAA
ATACCTGTTAGAGCAAGATATAAGACCGAATGTAATTGCGGGTACAAGTGCTGGCTC
TATGGTTGGTGCACTTTATTGCTCAGGACTTGAGATTGATGACATTTTACAATTCTT
CATCGATGTAAAACCTTTTTCTTGGAAGTTTACCCGTGCCCGTGCTGGCTTTATAGA
CCCGGCAAAATTATATCCTGAAGTGCTAAAATATATCCCCGAGGATAGCTTTGAGTA
CCTTCAACCTGAATTGCGCATTGTTGCCACCAACATGTTACTCGGTAAAGAGCATAT
ATTTAAAGATGGCTCCGTGATTAATGCCTTATTAGCATCAGCCAGCTACCCTTTAGT
TTTTTCTCCGATGATCATTGACGATCAAGTGTATTCAGATGGCGGTATTGTTAATCA
TTTCCCCGTGAGTGTCATTGAAGATGATTGCGATAAAATAATCGGCGTATACGTGTC
GCCCATTCGTCAGGTCGAAGCTGACGAACTCTCGAGTATAAAAGACGTGGTATTACG
TGCGTTCACGCTGCAGGGTAGTGGTGCTGAATTAGATAAACTATCGCAATGTGATGT
GCAAATTTATCCAGAAGCGCTATTGAATTACAATACGTTTGCAACCGATGAAAAATC
ATTACGGGAGATCTACCAGATTGGTTATGATGCTGCAAAAGATCAACATGACAACCT
TATGGCATTGAAAGAAAGTATCACCACCAGCGAGGTTAAAAAGAACGTCTTTAGCAA

FIG. 5-11

ATGGTTTGGTGATAAACTTGCTAGCAACAGCGGCAAATAGCGGCCCACACGGATTTA
TACACTAGGATAATGGGCGTTAATAGCCTCACTGTCGTTGTGTGGTCTCTAATTTTA
GCTAAATCTTGTGTTATACTGACTTCCTATTAATCATAAACGATTTATCACGGTAAA
CATGACTCAAATAAATAACCCGCTTCACGGCATGACACTCGAAAAAGTAATTAACAG
TCTCGTTGAACAATATGGCTGGGATGGTCTTGGATACTACATCAACATTCGTTGCTT
TACTGAAAATCCAAGTGTTAAGTCTAGTCTTAAATTTTTACGTAAAACCCCTTGGGC
ACGTGATAAAGTAGAAGCGCTATATATCAAAATGGTGACTGAAGGCTAACTGTCTCC
ACGCTAGCGAACCGCTGTTTATAGTTAATATAAGTACTATAAGCAGGGCTCGTTAAT
TCAGTATGTAATTAATCCTGAATACCTCCGCTTATTTCAACATTGTACTCTCTAGAT
AACACTCTCAACATTACACCTTCAACATCACAGCCTCCACATAACATCCGATGACAT
AGCCCTGTTATTTTTCACATTTATCTATATGCTATATATTTTAGCCATTTGATCAAT
TGAGTTAATTTCTGCAATGACAAAGATATACCATCATCCAGTACAAATTTATTATGA
AGATACCGACCATTCTGGTGTTGTTTACCACCCTAACTTTTTAAAATACTTTGAACG
TGCACGTGAGCATGTGATAAATAGTGACTTACTAGCAACATTGTGGAATGAACGCGG
TTTAGGTTTTGCGGTGTATAAAGCCAATATGACTTTTCAGGATGGGGTCGAATTTGC
TGAAGTGTGTGATATTCGCACTTCTTTTGTCCTAGACGGTAAGTACAAAACGATCTG
GCGCCAAGAAGTATGGCGTCCGAATGCGACTAGGGCTGCCGTTATCGGTGATATTGA
AATGGTGTGCTTAGACAAACAAAAACGTTTACAGCCCATCCCTGATGATGTGTTAGC
TGCAATGGTTAGTGAATAAATGGTTCATGCATAAATAGTTAATACATGATTCTGGCC
CGTCACGTTTACAGATAAGAGGCATCCGATGCCTCCTTCCTATTACCAATACTACTG
CTTATCCCTTTCTAACTATCTTTAGCGTCCATAACACACTGAGCATTTATTCTATTA
ATCAGTGATTGTGATTTAATTATCTTCTATATATGTAATTTAATGTAATTTTCAATT
TATTTTTAGCTACATTAAGGCTTACGAATGTACGCTAAAATGAGATGTCAGACTAAT
TTTAGCTTATTAATCTGTTAGCCGTTTATATTTTATAAAGATGGGATTTAACTTAAA

FIG. 5-12

TGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACTAAGTCCTG
AATTTTATATAAAGTTTAATCTGTTATTTTAGCGTTTACCTGGTCTTATCAGTGAGG
TTTATAGCCATTATTAGTGGGATTGAAGTGATTTTTAAAGCTATGTATATTATTGCA
AATATAAATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTCGAATTGATTG
GCATAAAATTTAAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCAGGT
AGATTTTTTTCGCCATTTAAGAGTACACTTGTACGCTAGGTTTTTGTTTAGTGTGCA
AATGAACGTTTTGATGAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGAGCA
ATAACGCAATGGCTAAAAAGAACACCACATCGATTAAGCACGCCAAGGATGTGTTAA
GTAGTGATGATCAACAGTTAAATTCTCGCTTGCAAGAATGTCCGATTGCCATCATTG
GTATGGCATCGGTTTTTGCAGATGCTAAAAACTTGGATCAATTCTGGGATAACATCG
TTGACTCTGTGGACGCTATTATTGATGTGCCTAGCGATCGCTGGAACATTGACGACC
ATTACTCGGCTGATAAAAAAGCAGCTGACAAGACATACTGCAAACGCGGTGGTTTCA
TTCCAGAGCTTGATTTTGATCCGATGGAGTTTGGTTTACCGCCAAATATCCTCGAGT
TAACTGACATCGCTCAATTGTTGTCATTAATTGTTGCTCGTGATGTATTAAGTGATG
CTGGCATTGGTAGTGATTATGACCATGATAAAATTGGTATCACGCTGGGTGTCGGTG
GTGGTCAGAAACAAATTTCGCCATTAACGTCGCGCCTACAAGGCCCGGTATTAGAAA
AAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTATGATCATCGACAAAT
TTAAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCATGCTAGGTAACG
TTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACTGTGTGGTTG
ATGCGGCATGCGCTGGCTCCCTTGCAGCTGTTAAAATGGCGATCTCAGACTTACTTG
AATATCGTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCATTCA
TGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTCCGT
TTGATGACGATTCAAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGTTTA
AACGTCTTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAGGTA
TCGGTACATCTTCAGATGGTCGTTTCAAATCTATTTACGCTCCACGCCCAGATGGCC
AAGCAAAAGCGCTAAAACGTGCTTATGAAGATGCCGGTTTTGCCCCTGAAACATGTG

FIG. 5-13

GTCTAATTGAAGGCCATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTGCTG
GCTTGACCAAACACTTTGGCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAGGCT
CAGTTAAATCGCAAATTGGTCATACTAAATCTGCGGCTGGCTCTGCGGGTATGATTA
AGGCGGCATTAGCGCTGCATCATAAAATCTTACCTGCAACGATCCATATCGATAAAC
CAAGTGAAGCCTTGGATATCAAAAACAGCCCGTTATACCTAAACAGCGAAACGCGTC
CTTGGATGCCACGTGAAGATGGTATTCCACGTCGTGCAGGTATCAGCTCATTTGGTT
TTGGCGGCACCAACTTCCATATTATTTAGAAGAGTATCGCCCAGGTCACGATAGCG
CATATCGCTTAAACTCAGTGAGCCAAACTGTGTTGATCTCGGCAAACGACCAACAAG
GTATTGTTGCTGAGTTAAATAACTGGCGTACTAAACTGGCTGTCGATGCTGATCATC
AAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCATTAAAAACCCCATCCGTTA
ACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAGCGATCGCGATGATTG
ATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACATGGTCAGTACCTA
CCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGGTTGCGCTAT
TCTCAGGGCAAGGTTCGCAATACGTGAACATGGGTCGTGAATTAACCTGTAACTTCC
CAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTTTAG
GCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTAAGC
TACAAGAAGAGCAATTACGTTTAACGCAACATGCGCAACCAGCGATTGGTAGTTTGA
GTGTTGGTCTGTTCAAAACGTTTAAGCAAGCAGGTTTTAAAGCTGATTTTGCTGCCG
GTCATAGTTTCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAAGCG
ATTACATGATGTTAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAACAAG
ATTTTGATGCAGGTAAGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTGTGA
TCATTGATACCCTTGATGATGTCTCTATTGCTAACTTCAACTCGAATAACCAAGTTG
TTATTGCTGGTACTACGGAGCAGGTTGCTGTAGCGGTTACAACCTTAGGTAATGCTG
GTTTCAAAGTTGTGCCACTGCCGGTATCTGCTGCGTTCCATACACCTTTAGTTCGTC
ACGCGCAAAAACCATTTGCTAAAGCGGTTGATAGCGCTAAATTTAAAGCGCCAAGCA
TTCCAGTGTTTGCTAATGGCACAGGCTTGGTGCATTCAAGCAAACCGAATGACATTA

FIG. 5-14

AGAAAAACCTGAAAAACCACATGCTGGAATCTGTTCATTTCAATCAAGAAATTGACA
ACATCTATGCTGATGGTGGCCGCGTATTTATCGAATTTGGTCCAAAGAATGTATTAA
CTAAATTGGTTGAAAACATTCTCACTGAAAAATCTGATGTGACTGCTATCGCGGTTA
ATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCCAAGCTGCGCTGCAAATGG
CAGTGCTTGGTGTCGCATTAGACAATATTGACCCGTACGACGCCGTTAAGCGTCCAC
TTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAGCGTCTTATGTTA
GTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGACTGTTAAGC
AAGCGAAAGCTGTACCTGCTGTTGTGTCACAACCACAAGTGATTGAAAAGATCGTTG
AAGTTGAAAAGATAGTTGAACGCATTGTCGAAGTAGAGCGTATTGTCGAAGTAGAAA
AAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAAATAATCAAGACGTTA
ACAGCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGACTCATAGCAGTGATGCTG
ACCTTGTTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGCAAT
TATTAAATGTACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAGTGC
AGAACGTACTTGCTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTACAT
TGTCTATGTATAACGAGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACCTGA
ACAATCAGACGAGCAACATGAACACCATGCTTACTGGTGCTGAAGCTGATGTGCTAG
CAACCCCAATAACTCAGGTAGTGAATACAGCCGTTGCCACTAGTCACAAGGTAGTTG
CTCCAGTTATTGCTAATACAGTGACGAATGTTGTATCTAGTGTCAGTAATAACGCGG
CGGTTGCAGTGCAAACTGTGGCATTAGCGCCTACGCAAGAAATCGCTCCAACAGTCG
CTACTACGCCAGCACCCGCATTGGTTGCTATCGTGGCTGAACCTGTGATTGTTGCGC
ATGTTGCTACAGAAGTTGCACCAATTACACCATCAGTTACACCAGTTGTCGCAACTC
AAGCGGCTATCGATGTAGCAACTATTAACAAAGTAATGTTAGAAGTTGTTGCTGATA
AAACCGGTTATCCAACGGATATGCTGGAACTGAGCATGGACATGGAAGCTGACTTAG
GTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAGTACAGGAATTGATCCCTG
ACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCACGCTTGGTGAGATTG
TCGATTACATGAATTCAAAAGCCCAGGCTGTAGCTCCTACAACAGTACCTGTAACAA

FIG. 5-15

GTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCCACATCCAAAACGTAA
TGTTAGAAGTGGTTGCAGACAAAACCGGTTACCCAACAGACATGCTAGAACTGAGCA
TGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAGGTG
CAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTGAAT
TACGCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTGAAA
GTGCGCCAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATTTGA
ACCACATTCAAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAACTG
ACATGCTAGAACTTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCAAAC
GTGTGGAAATATTAGGCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAAACC
CAGAAGACCTCGCTGAATTACGCACGCTAGGTGAAATCGTTAGTTACATGCAAAGCA
AAGCGCCAGTCGCTGAGAGTGCGCCAGTAGCGACGGCTTCTGTAGCAACAAGCTCTG
CACCGTCTATCGATTTAAACCATATCCAAACAGTGATGATGGAAGTGGTTGCAGACA
AAACCGGTTATCCAGTAGACATGTTAGAACTTGCTATGGACATGGAAGCTGACCTAG
GTATCGATTCAATCAAGCGTGTAGAAATTTTAGGTGCGGTACAGGAAATCATTACTG
ACTTACCTGAGCTTAACCCTGAAGATCTTGCTGAACTACGTACATTAGGTGAAATCG
TTAGTTACATGCAAAGCAAAGCGCCCGTAGCTGAAGCGCCTGCAGTACCTGTTGCAG
TAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCACCGTCTATCGATTTAGACCACA
TCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTGGTTATCCTGCCAATATGC
TTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATTCAATCAAGCGTGTTG
AAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAACTAAACCCAGAAG
ACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAAGCAAGGCGA
GTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAGATGCAT
TTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAATTTA
AACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAATAA
GCCAAGATTGTAAAGGTGCTAACGCCTTAATCGTAGCTGATGGCACTGATAATGCTG

FIG. 5-16

TGTTACTTGCAGACCACCTATTGCAAACTGGCTGGAATGTAACTGCATTGCAACCAA
CTTGGGTAGCTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGACTT
TAAATGGCGTTGATGAAACTGAAATCAACAACATTATTACTGCTAACGCACAATTGG
ATGCAGTTATCTATCTGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCACAAG
CATCTAAGCAAGGCCTGATGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAACTC
AAGCCGCTAAAGTGCGTGGCGCCTTTATGATTGTTACTCAGCAGGGTGGTTCATTAG
GTTTTGATGATATCGATTCTGCTACAAGTCATGATGTGAAAACAGACCTAGTACAAA
GCGGCTTAAACGGTTTAGTTAAGACACTGTCTCACGAGTGGGATAACGTATTCTGTC
GTGCGGTTGATATTGCTTCGTCATTAACGGCTGAACAAGTTGCAAGCCTTGTTAGTG
ATGAACTACTTGATGCTAACACTGTATTAACAGAAGTGGGTTATCAACAAGCTGGTA
AAGGCCTTGAACGTATCACGTTAACTGGTGTGGCTACTGACAGCTATGCATTAACAG
CTGGCAATAACATCGATGCTAACTCGGTATTTTTAGTGAGTGGTGGCGCAAAAGGTG
TAACTGCACATTGTGTTGCTCGTATAGCTAAAGAATATCAGTCTAAGTTCATCTTAT
TGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAAGTGGTATTACTGATG
AAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAGGTGATAAACCAA
CACCCGTTAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTGAAATTGCGC
AAACCTTGTCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTGCAGATG
TAACTAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCGGTG
CAATCACTGGCATCATTCATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGCAAA
AAACACTGAGTGATTTTGAGTCTGTTTACAGCACTAAAATTGACGGTTTGTTATCGC
TACTATCAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAGCGG
CTGGTTTCTACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCTTAA
ATAAAACCGCATACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCTTTA
ACTGGGGTCCTTGGGACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTGACC
AACGTGGTGTTTACATTATTCCACTTGATGCAGGTGCACAGTTATTGCTGAATGAAC

FIG. 5-17

TAGCCGCTAATGATAACCGTTGTCCACAAATCCTCGTGGGTAATGACTTATCTAAAG
ATGCTAGCTCTGATCAAAAGTCTGATGAAAAGAGTACTGCTGTAAAAAAGCCACAAG
TTAGTCGTTTATCAGATGCTTTAGTAACTAAAAGTATCAAAGCGACTAACAGTAGCT
CTTTATCAAACAAGACTAGTGCTTTATCAGACAGTAGTGCTTTTCAGGTTAACGAAA
ACCACTTTTTAGCTGACCACATGATCAAAGGCAATCAGGTATTACCAACGGTATGCG
CGATTGCTTGGATGAGTGATGCAGCAAAAGCGACTTATAGTAACCGAGACTGTGCAT
TGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTAAAGGTGTGGTTTTTGATGGCA
ATGAGGCGGCGGATTACCAAATCCAATTGTCGCCTGTGACAAGGGCGTCAGAACAGG
ATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAAGTGACGGTAAACCTG
TGTTTCATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTAATGCTGTGAAGG
TAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAACTGATGAAG
CACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGGGCATTA
AGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTCAGATAACCGATG
TTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCAATG
ATTTGGTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTAGCT
TACCTTCGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAGTAT
TTTATCTGCAACTTAATGTTGTTGAGCATGATCTATTGGGTTCACGCGGCAGTAAAG
CCCGTTGTGATATTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGAAAT
CAGCGCAAGTCAGTGTCAGTGACATTTTGAACGATATGTCATGATCGAGTAAATAAT
AACGATAGGCGTCATGGTGAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTAACA
ATATTAATAGCTAAACGCGGTTGCTTTAAACCAAGTAAACAAGTGCTTTTAGCTATT
ACTATTCCAAACAGGATATTAAAGAGAATATGACGGAATTAGCTGTTATTGGTATGG
ATGCTAAATTTAGCGGACAAGACAATATTGACCGTGTGGAACGCGCTTTCTATGAAG
GTGCTTATGTAGGTAATGTTAGCCGCGTTAGTACCGAATCTAATGTTATTAGCAATG
GCGAAGAACAAGTTATTACTGCCATGACAGTTCTTAACTCTGTCAGTCTACTAGCGC

FIG. 5-18

AAACGAATCAGTTAAATATAGCTGATATCGCGGTGTTGCTGATTGCTGATGTAAAAA
GTGCTGATGATCAGCTTGTAGTCCAAATTGCATCAGCAATTGAAAAACAGTGTGCGA
GTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATCAAGTAGCTGATTTAGTTA
ATAACCAAGACTGTCCTGTGGCTGTAATTGGCATGAATAACTCGGTTAATTTATCTC
GTCATGATCTTGAATCTGTAACTGCAACAATCAGCTTTGATGAAACCTTCAATGGTT
ATAACAATGTAGCTGGGTTCGCGAGTTTACTTATCGCTTCAACTGCGTTTGCCAATG
CTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCGTAAATG
CTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTGCAGCAAGCTA
GCATAACTGCAGAGCAGGTTGGTTTGTTAGAAGTGTCAGCAGTCGCTGATTCGGCAA
TCGCATTGTCTGAAAGCCAAGGTTTAATGTCTGCTTATCATCATACGCAAACTTTGC
ATACTGCATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTTTTCACAGG
TCGCAGGTTTATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGATTA
AAGATTGGCAACAACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCATTCT
ATATGCCTGTAGATGCTCGACCTTGGTTCCCACATGCTGATGGCTCTGCACACATTG
CCGCTTATAGTTGTGTGACTGCTGACAGCTATTGTCATATTCTTTTACAAGAAAACG
TCTTACAAGAACTTGTTTTGAAAGAAACAGTCTTGCAAGATAATGACTTAACTGAAA
GCAAGCTTCAGACTCTTGAACAAAACAATCCAGTAGCTGATCTGCGCACTAATGGTT
ACTTTGCATCGAGCGAGTTAGCATTAATCATAGTACAAGGTAATGACGAAGCACAAT
TACGCTGTGAATTAGAAACTATTACAGGGCAGTTAAGTACTACTGGCATAAGTACTA
TCAGTATTAAACAGATCGCAGCAGACTGTTATGCCCGTAATGATACTAACAAAGCCT
ATAGCGCAGTGCTTATTGCCGAGACTGCTGAAGAGTTAAGCAAAGAAATAACCTTGG
CGTTTGCTGGTATCGCTAGCGTGTTTAATGAAGATGCTAAAGAATGGAAAACCCCGA
AGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGGCTGCTAACAGCACACAGA
ATGGTGTCACCTTCATGTACCCAGGTATTGGTGCTACATATGTTGGTTTAGGGCGTG
ATCTATTTCATCTATTCCCACAGATTTATCAGCCTGTAGCGGCTTTAGCCGATGACA

FIG. 5-19

TTGGCGAAAGTCTAAAAGATACTTTACTTAATCCACGCAGTATTAGTCGTCATAGCT
TTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAACTTAGCCAATATCGCTG
AAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTGCCG
TTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAGCAC
TAGGCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGCACAATCGAATACCT
TTAATCATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGGATG
ATGTAGCTAACGGTACGTTCGAGCAGATCTGGGAAACCTATACCATTAAGGCAACGA
TTGAACAGGTCGAAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTATCA
ATACACCTGATAGCTTGTTGTTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCATTA
AGAATTTAGGTGTGCGTGCAATGGCATTGAATATGGCGAACGCAATTCACAGCGCGC
CAGCTTATGCCGAATACGATCATATGGTTGAGCTATACCATATGGATGTTACTCCAC
GTATTAATACCAAGATGTATTCAAGCTCATGTTATTTACCGATTCCACAACGCAGCA
AAGCGATTTCCCACAGTATTGCTAAATGTTTGTGTGATGTGGTGGATTTCCCACGTT
TGGTTAATACCTTACATGACAAAGGTGCGCGGGTATTCATTGAAATGGGTCCAGGTC
GTTCGTTATGTAGCTGGGTAGATAAGATCTTAGTTAATGGCGATGGCGATAATAAAA
AGCAAAGCCAACATGTATCTGTTCCTGTGAATGCCAAAGGCACCAGTGATGAACTTA
CTTATATTCGTGCGATTGCTAAGTTAATTAGTCATGGCGTGAATTTGAATTTAGATA
GCTTGTTTAACGGGTCAATCCTGGTTAAAGCAGGCCATATAGCAAACACGAACAAAT
AGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTAGTTGAAATATGGATT
TAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTAATTTGTTCCCGG
GCTCACAAGCACCGGATCAATTTTGGCAGCAATTGCTTGAACAACAAGATTGCCGCA
GTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCAACAAAG
GTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATTTTG
ATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTAATC
AATGGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCAGTA

FIG. 5-20

CTGCACTAGAAAACTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAATCAT
CTAATCAGCTGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGGCGG
TATTACATCCTGATTTTCAATTAACGCATTACACAGCACCGAAAAAAACACATGCTG
ACAATGCATTAGTAGCAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTCTTG
GTGGTTCACATTTTGCACTGGATGCGGCTTGTGCTTCATCTTGTTATAGCGTTAAGT
TAGCGTGTGATTACCTGCATACGGGTAAAGCCAACATGATGCTTGCTGGTGCGGTAT
CTGCAGCAGATCCTATGTTCGTAAATATGGGTTTCTCGATATTCCAAGCTTACCCAG
CTAACAATGTACATGCCCCGTTTGACCAAAATTCACAAGGTCTATTTGCCGGTGAAG
GCGCGGGCATGATGGTATTGAAACGTCAAAGTGATGCAGTACGTGATGGTGATCATA
TTTACGCCATTATTAAAGGCGGCGCATTATCGAATGACGGTAAAGGCGAGTTTGTAT
TAAGCCCGAACACCAAGGGCCAAGTATTAGTATATGAACGTGCTTATGCCGATGCAG
ATGTTGACCCGAGTACAGTTGACTATATTGAATGTCATGCAACGGGCACACCTAAGG
GTGACAATGTTGAATTGCGTTCGATGGAAACCTTTTTCAGTCGCGTAAATAACAAAC
CATTACTGGGCTCGGTTAAATCTAACCTTGGTCATTTGTTAACTGCCGCTGGTATGC
CTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTCCTGCAACGATTA
ACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGCAAATGCCAA
CGACGACTGTGTCTTGGCCAACAACTCCGGGTGCCAAGGCAGATAAACCGCGTACCG
CAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTTGGTATTACAACAGC
CAACGCAAACACTCGAGACTAATTTTAGTGTTGCTAAACCACGTGAGCCTTTGGCTA
TTATTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAACCT
TATTAAATAATAATCAAAATACCTTCCGTGAATTACCAGAACAACGCTGGAAAGGCA
TGGAAAGTAACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAGGCA
GTTACGTTGAACAGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATGAAA
AAGATTGCTTGATCCCGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTGCGA
AAGACGGAGGTCTAGTTGAAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCATGG

FIG. 5-21

AACTGGAATTACATCAGTATCGTGGTCGCGTTAATCTAACCACCCAAATTGAAGACA
GCTTATTACAGCAAGGTATTAACCTGACTGTTGAGCAACGTGAAGAACTGACCAATA
TTGCTAAAGACGGTGTTGCCTCGGCTGCACAGCTAAATCAGTATACGAGTTTCATTG
GTAATATTATGGCGTCACGTATTTCGGCGTTATGGGATTTTTCTGGTCCTGCTATTA
CCGTATCGGCTGAAGAAAACTCTGTTTATCGTTGTGTTGAATTAGCTGAAAATCTAT
TTCAAACCAGTGATGTTGAAGCCGTTATTATTGCTGCTGTTGATTTGTCTGGTTCAA
TTGAAAACATTACTTTACGTCAGCACTACGGTCCAGTTAATGAAAAGGGATCTGTAA
GTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCAACAATATTCTTGATCAGC
AACAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTCGTTAAACCGTCATCGCAAG
TCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTGCCCCTGGTAGCA
ATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACACTTGCTGGTATCAGTG
CTGCTGATGTAGCTAGTGTTGAAGCACATGCAAGTGGTTTTAGTGCCGAAAATAATG
CTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGAAAG
CCAATATTGGTCATACGTTTAATGCCTCGGGTATGGCGAGTATTATTAAAACGGCGC
TGCTGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTAACG
GTCTAGGTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAGCGC
ATCAAGTTGCACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCCACAGTTAGTTA
AAACCATCAAACTCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCGAGTT
CATCTTTACACGCTATTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTAACC
AGCCAGTGATGATGGATAACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCAATG
AGTATGTGGTGACTGGAGCTGCTAACACTCAAGCTTCTAACATTCAAGCATCTCATG
TTCAAGCGTCAAGTCATGCACAAGAGATAGCACCAAACCAAGTTCAAAATATGCAAG
CTACAGCAGCCGCTGTAAGTTCACCCCTTTCTCAACATCAACACACAGCGCAGCCCG
TAGCGGCACCGAGCGTTGTTGGAGTGACTGTGAAACATAAAGCAAGTAACCAAATTC
ATCAGCAAGCGTCTACGCATAAAGCATTTTTAGAAAGTCGTTTAGCTGCACAGAAAA

FIG. 5-22

ACCTATCGCAACTTGTTGAATTGCAAACCAAGCTGTCAATCCAAACTGGTAGTGACA
ATACATCTAACAATACTGCGTCAACAAGCAATACAGTGCTAACAAATCCTGTATCAG
CAACGCCATTAACACTTGTGTCTAATGCGCCTGTAGTAGCGACAAACCTAACCAGTA
CAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTCAGATAAAAGGACCTG
TTGGTTACAACTATCCACCGCTGCAGTTAATTGAACGTTATAATAAACCAGAAAACG
TGATTTACGATCAAGCTGATTTGGTTGAATTCGCTGAAGGTGATATTGGTAAGGTAT
TTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGCCAACCT
CAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAATACA
AGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAATTG
ATGGTCAGATCCCTTGGTCTGTTGCCGTCGAATCAGGCCAGTGTGATTTGATGTTGA
TTTCATATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTACTTG
ATTGTGAATTAACTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTTACG
AGATCCACATTGATTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCCATT
ACGATTGTTACGTAGGGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTGGTT
TCTTTACTGACGAAGAACTTTCTGATGGTAAAGGCGTTATTCATAACGACAAAGACA
AAGCTGAGTTTAGCAATGCTGTTAAATCATCATTCACGCCGTTATTACAACATAACC
GTGGTCAATACGATTATAACGACATGATGAAGTTGGTTAATGGTGATGTTGCCAGTT
GTTTTGGTCCGCAATATGATCAAGGTGGCCGTAATCCATCATTGAAATTCTCGTCTG
AGAAGTTCTTGATGATTGAACGTATTACCAAGATAGACCCAACCGGTGGTCATTGGG
GACTAGGCCTGTTAGAAGGTCAGAAAGATTTAGACCCTGAGCATTGGTATTTCCCTT
GTCACTTTAAAGGTGATCAAGTAATGGCTGGTTCGTTGATGTCGGAAGGTTGTGGCC
AAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGCATACCAATGTGAACAACGCTC
GTTTCCAACCACTACCAGGTGAATCACAAACGGTACGTTGTCGTGGGCAAGTACTGC
CACAGCGCAATACCTTAACTTACCGTATGGAAGTTACTGCGATGGGTATGCATCCAC
AGCCATTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAGTGGTTGTTGATT

FIG. 5-23

TCAAAAACTTGAGCGTGATGATCAGCGAACAAGATGAGCATTCAGATTACCCTGTAA
CACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAGTAGCAC
CAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTTGAACCGTTTA
AGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAAGCA
AAGGTGTGACACCGATTAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATAGAG
TGCCTAACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTGCGACGGGTAATA
TTTCTAACTGTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCCACCTCGTA
CACCTTGTGGCGATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAACGTC
TTGATCTTAAAAATCCATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACGCTT
GGTACTTTACTAAAAACAGCCATGAAAACTGGATGCCTTATTCATTAATCATGGAAA
TTGCATTGCAACCAAATGGCTTTATTTCTGGTTACATGGGCACGACGCTTAAATACC
CTGAAAAAGATCTGTTCTTCCGTAACCTTGATGGTAGCGGCACGTTATTAAAGCAGA
TTGATTTACGCGGCAAGACCATTGTGAATAAATCAGTCTTGGTTAGTACGGCTATTG
CTGGTGGCGCGATTATTCAAAGTTTCACGTTTGATATGTCTGTAGATGGCGAGCTAT
TTTATACTGGTAAAGCTGTATTTGGTTACTTTAGTGGTGAATCACTGACTAACCAAC
TGGGCATTGATAACGGTAAAACGACTAATGCGTGGTTTGTTGATAACAATACCCCCG
CAGCGAATATTGATGTGTTTGATTTAACTAATCAGTCATTGGCTCTGTATAAAGCGC
CTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGATGAACTTTATCGATACAG
TGTCAGTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATGTTTATGGCGAACGTA
CGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAGATCCGGTGATGC
CAGGTTCATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATGCGCTTAAAA
ATGATTTGGGTGGCAAGTTTGCTAACCCACGTTTCATTGCGCCGATGACGCAAGTTG
ATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACTGGACGTGC
ATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGAATC
TGTCTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTGTTG

FIG. 5-24

AAGCGTAAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCTTTG
CACGCCGTGAATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAGCAA
GCTTACTTTAATCAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAGTTA
ATAGACAAAATAATTTAGCTGTGGAATGAATATAGTAAGTAATCATTCGGCAGCTAC
AAAAAAGGAATTAAGAATGTCGAGTTTAGGTTTTAACAATAACAACGCAATTAACTG
GGCTTGGAAAGTAGATCCAGCGTCAGTTCATACACAAGATGCAGAAATTAAAGCAGC
TTTAATGGATCTAACTAAACCTCTCTATGTGGCGAATAATTCAGGCGTAACTGGTAT
AGCTAATCATACGTCAGTAGCAGGTGCGATCAGCAATAACATCGATGTTGATGTATT
GGCGTTTGCGCAAAAGTTAAACCCAGAAGATCTGGGTGATGATGCTTACAAGAAACA
GCACGGCGTTAAATATGCTTATCATGGCGGTGCGATGGCAAATGGTATTGCCTCGGT
TGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCTGTTATGTTCATTTGGTGCTGCAGG
TCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCGTATTCAAGCTGAATTACCAAA
TGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGAAGAAGCATTAGAGCGTGG
CGCGGTTGAACGTTTCCTAAAACTTGGCGTCAAGACGGTAGAGGCTTCAGCTTACCT
TGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAACTAAAAACGCAGA
TGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTACCGAAGTTGG
TCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGAACAAAA
TAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGATAT
TACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATTATT
ACCGACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCCTGC
ATTACGTGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGCATT
TAACATGGGCGCGGCTTATATCGTTCTGGGTTCTGTGAATCAGGCGTGTGTTGAAGC
GGGTGCATCTGAATATACTCGTAAACTGTTATCGACAGTTGAAATGGCTGATGTGAC
TATGGCACCTGCTGCAGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAAAACG
CGGTTCTATGTTCGCGATGCGTGCGAAGAAACTGTATGACTTGTATGTGGCTTATGA

FIG. 5-25

CTCGATTGAAGATATCCCAGCTGCTGAACGTGAGAAGATTGAAAAACAAATCTTCCG
TGCAAACCTAGACGAGATTTGGGATGGCACTATCGCTTTCTTTACTGAACGCGATCC
AGAAATGCTAGCCCGTGCAACGAGTAGTCCTAAACGTAAAATGGCACTTATCTTCCG
TTGGTATCTTGGCCTTTCTTCACGCTGGTCAAACACAGGCGAGAAGGGACGTGAAAT
GGATTATCAGATTTGGGCAGGCCCAAGTTTAGGTGCATTCAACAGCTGGGTGAAAGG
TTCTTACCTTGAAGACTATACCCGCCGTGGCGCTGTAGATGTTGCTTTGCATATGCT
TAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTTGAAATTGCAAGGTGTTAGCTT
AAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATGTTACTTGATGATATGTGA
ATTAATTAAAGCGCCTGAGGGCGCTTTTTTTGGTTTTTAACTCAGGTGTTGTAACTC
GAAATTGCCCCTTTCAAGTTAGATCGATTACTCACTCACAATATGTTGATATCGCAC
TTGCCATATACTTGCTCATCCAAAGCCCTATATTGATAATGGTGTTAATAGTCTTTA
ATATCCGAGTCTTTCTTCAGCATAATACTAATATAGAGACTCGACCAATGTTAAACA
CAACAAAGAATATATTCTTGTGTACTGCCTTATTATTAACGAGTGCGAGTACGACAG
CTACTACGCTAAACAATTCGATATCAGCAATTGAACAACGTATTTCTGGTCGTATCG
GTGTGGCTGTTTTAGATACGCAAAATAAACAAACGTGGGCTTACAATGGTGATGCAC
ATTTTCCGATGATGAGTACATTCAAAACCCTCGCTTGCGCGAAAATGCTAAGTGAAT
CGACAAATGGTAATCTGGATCCCAGTACTAGCTCATTGATAAAGGCTGAAGAATTAA
TCCCTTGGTCACCAGTCACTAAAACGTTTGTGAATAACACTATTACAGTGGCGAAAG
CGTGTGAAGCAACAATGCTGACCAGTGATAATACCGCGGCTAATATTGTTTTACAGT
ATATCGGAGGCCCTCAAGGCGTTACTGCATTCTTGCGAGAAATTGGTGATGAAGAGA
GTCAGTTAGATCGTATAGAACCTGAATTGAATGAAGCTAAGGTCGGAGACTTGCGTG
ATACCACGACACCGAAAGCCATAGTTACCACGCTCAACAAACTACTACTTGGTGATG
TTCTACTTGATTTGGATAAAAACCAACTTAAAACATGGATGCAAAATAATAAAGTGT
CAGATCCTTTACTGCGTTCTATATTACCGCAAGGCTGGTTTATTGCCGACCGCTCAG
GTGCGGGTGGTAATGGTTCTCGAGGTATAACTGCTATGCTTTGGCACTCCGAGCGTC

FIG. 5-26

AACCGCTAATCATCAGTATTTATTTAACCGAAACTGAGTTAGCAATGGCAATGCGCA
ATGAGATTATTGTTGAGATCGGTAAGCTGATATTCAAAGAATACGCGGTGAAATAAT
AAGTTATTTTTTGATAATACTTTAACGAGCGTAGCTATCGAAGTGAGGGCGTCAATT
AGACACCTTTGCTTCCCCTACAAAATCTAATGTGTATTACCTCGGCTAGTACAATTG
CCCTAAGTTATTTCTGTCCAGCTTTGGCTTAGTGCAATTGCGTTAGCCAATGTGAAC
ACCAAGGGACTTTGTCGTACCATAACTACCAAGCGACTTTGTCGTTTTTATCTTTTC
TTAGACAAACAGAGGTTAAATGAGTGACGCCTTCCAAATCACAGGAATGAATCCGCA
TTTCAATAAAATCTAACCCGTACCAACTCCGTACAAGTTGATCTTTAGTTGTTTAAA
ATCTATAATAAATTCAATTACGGAATTAATCCGTACAACTGGAGGTTTTATGGCTAC
TGCAAGACTTGATATCCGTTTGGATGAAGAAATCAAAGCTAAGGCTGAGAAAGCATC
AGCTTTACTCGGCTTAAAAAGTTTAACCGAATACGTTGTTCGCTTAATGGACGAAGA
TTCAACTAAAGTAGTTTCTGAGCATGAGAGTATTACCGTTGAAGCGAATGTATTCGA
CCAATTTATGGCTGCTTGTGATGAAGCGAAAGCCCCAAATAAAGCATTACTTGAAGC
CGCTGTATTTACTCAGAATGGTGAGTTTAAGTGAGTTATTCCAAACGTTTCAAAGAA
CTGGATAAATCAAAACATGACAGAGCATCATTTGACTGTGGCGAAAAAGAGCTAAAT
GATTTTATCCAAACTCAAGCAGCCAAACATATGCAAGCAGGTATTAGCCGCACTCTG
GTTTTACCTGCTTCTGCGCCGTTACCAAACAAAAAATATCCAATTTGCTCATTTTAT
AGTATCGCGCCAAGCTCAATTAGCCGCGATACGTTACCACAAGCAATGGCTAAAAAG
TTACCACGTTATCCTATCCCTGTTTTTCTTTTGGCTCAACTTGCCGTCCATAAAGAG
TTTCATGGGAGTGGGTTAGGCAAAGTTAGCTTAATTAAAGCGTTAGAGTACCTTTGG
GAAATTAACTCTCACATGAGAGCTTACGCCATCGTTGTTGATTGTTTAACTGAACAA
GCTGAGTCATTCTACGCTAAATATGGTTTCGACGTTCTCTGCGAAATAAATGGTCGA
GTAAGAATGTTCATATCAATGAAAACAGTCAATCAGTTATTCACTTAACAGTAAGAG
TTAGTATAACAGTTGTATGAATTAAATTTATTATATTCGGTAATCTCATTGCGATCA
CGCTAGAAGTGCGAGCGGGTCAGACCGAGGCCACAATAGCAGCCGTTACGTTTAGGG

FIG. 5-27

GATGACTTAAAAAGATAACTACTACGTCAGTGGCGATCCTAGAGGATTAAAGGTTTA
TGATTCACAACATTTATTTATTGTGCTTAATTTTTCTATCCAATATGCGCAAGCTG
TAAATATCACTGAAGTAGACTTTTATGTCAGTGATGATATCCCTAAAGATGTTGCCA
AATTAAAGATAGGTGAATCCATAACGAACTCCAGCCTTATTCTAAGTAACTCATCTA
TTCCACTCTCGCGGGAGACGGGTAACATATATTACTCTTCATCAATTGCTAACTTGA
ACTATGACTCGATAGAATTTGTTATGGCTCAATTGATGGCCGAAGATTCCAGCCTTT
ACAAGATGCTGGTAAATAGCGATAGGTTGTCCGTGCTAGTAATGACATCTTCCCAGT
CCACAGATCTCTATGGCTCGACTTACTCGGCTTATTTTCCTAATGTTGCGGTCATCG
ATTTGAATTGTGACTCGCTAACTTTAGAACATGAGCTCGGCCATCTATACGGAGCTG
AACATGAAGAAATATATGACGACTATGTCTTCTATGCTGCGATATGTGGAGACTATA
CGACTATCATGAACTCTATGCAGCCTGAAATGAAAGAAAAACAAATGATAAAGGCAT
ATTCATTCCCTGAATTAAAAGTGGATGGCTTGCAGTGCGGAAATGAAAATACGAATA
ACAAAAAGGTTATTTTAGACAATATTGGTCGGTTTAGATAGGATTGGGATATTATTC
TCATTCGGCTCTACTTAGTGCTGTTATTATGAGTGCCAGTGCTTCTATCTACGATAT
TGGTCTTAACAAGTATTTATCTATAGACGCTAAGGTGTTATGTATTTAAGGGATGTT
CAAGATGAAACTAGGTGTAAACGATGTATAGTTGTATAACATTTTTTCAACGGTTGG
AACGTTCGATTCTATCGGGTAACAAGACCGCGACGATCCGCGATAAGTCCGATAGTC
ATTACTTAGTTGGTCAGATGTTAGATGCTTGTACTCACGAAGATAATCGGAAAATGT
GTCAAATAGAAATACTGAGCATTGAATATGTGACGTTTAGTGAATTAAACCGTGCGC
ACGCCAATGCTGAAGGTTTACCGTTTTTGTTTATGCTTAAGTGGATAGTTCGAAAGA
TTTATCCGACTTCAAATGATTTATTTTTCATAAGTTTCAGAGTTGTAACTATCGATA
TCTTATAAGTCTTAGTGCACAAAACAGAACTATTTATAGCGCTCAAGAAGGCGATAA
TTTGATAATGAATTATCGCCTTGTTACTATTAAGAGACTTTAAATGACTGAGATATA
AGATATGACACGGAAGAACATATTGATCACAGGCGCAAGTTCAGGGTTGGGCCGAGG
TATGGCCATCGAATTTGCAAAATCAGGTCATAACTTAGCACTTTGTGCACGTAGACT

FIG. 5-28

TGATAATTTAGTTGCACTGAAAGCAGAACTCTTAGCCCTCAATCCTCACATCCAAAT
CGAAATAAAACCTCTTGATGTCAATGAACATGAACAAGTCTTCACTGTTTTCCATGA
ATTCAAAGCTGAATTTGGTACGCTTGATCGTATTATTGTTAATGCTGGATTAGGCAA
GGGTGGATCC

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FIG. 5-29

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AAATGCAATTAATTATGGCGTAAATAGAGTGAAAACATGGCTAATATTCACTAAGTC
CTGAATTTTATATAAAGTTTAATCTGTTATTTAGCGTTTACCTGGTCTTATCAGTG
AGGTTTATAGCCATTATTAGTGGGATTGAAGTGATTTTTAAAGCTATGTATATTATT
GCAAATATAAATTGTAACAATTAAGACTTTGGACACTTGAGTTCAATTTCGAATTGA
TTGGCATAAAATTTAAAACAGCTAAATCTACCTCAATCATTTTAGCAAATGTATGCA
GGTAGATTTTTTTCGCCATTTAAGAGTACACTTGTACGCTAGGTTTTTGTTTAGTGT
GCAAATGAACGTTTTGATGAGCATTGTTTTTAGAGCACAAAATAGATCCTTACAGGA
GCAATAACGCAATGGCTAAAAAGAACACCACATCGATTAAGCACGCCAAGGATGTGT
TAAGTAGTGATGATCAACAGTTAAATTCTCGCTTGCAAGAATGTCCGATTGCCATCA
TTGGTATGGCATCGGTTTTTGCAGATGCTAAAAACTTGGATCAATTCTGGGATAACA
TCGTTGACTCTGTGGACGCTATTATTGATGTGCCTAGCGATCGCTGGAACATTGACG
ACCATTACTCGGCTGATAAAAAAGCAGCTGACAAGACATACTGCAAACGCGGTGGTT
TCATTCCAGAGCTTGATTTTGATCCGATGGAGTTTGGTTTACCGCCAAATATCCTCG
AGTTAACTGACATCGCTCAATTGTTGTCATTAATTGTTGCTCGTGATGTATTAAGTG
ATGCTGGCATTGGTAGTGATTATGACCATGATAAAATTGGTATCACGCTGGGTGTCG
GTGGTGGTCAGAAACAAATTTCGCCATTAACGTCGCGCCTACAAGGCCCGGTATTAG
AAAAAGTATTAAAAGCCTCAGGCATTGATGAAGATGATCGCGCTATGATCATCGACA
AATTTAAAAAAGCCTACATCGGCTGGGAAGAGAACTCATTCCCAGGCATGCTAGGTA
ACGTTATTGCTGGTCGTATCGCCAATCGTTTTGATTTTGGTGGTACTAACTGTGTGG
TTGATGCGGCATGCGCTGGCTCCCTTGCAGCTGTTAAAATGGCGATCTCAGACTTAC
TTGAATATCGTTCAGAAGTCATGATATCGGGTGGTGTATGTTGTGATAACTCGCCAT
TCATGTATATGTCATTCTCGAAAACACCAGCATTTACCACCAATGATGATATCCGTC
CGTTTGATGACGATTCAAAAGGCATGCTGGTTGGTGAAGGTATTGGCATGATGGCGT
TTAAACGTCTTGAAGATGCTGAACGTGACGGCGACAAAATTTATTCTGTACTGAAAG
GTATCGGTACATCTTCAGATGGTCGTTTCAAATCTATTTACGCTCCACGCCCAGATG
GCCAAGCAAAAGCGCTAAAACGTGCTTATGAAGATGCCGGTTTTGCCCCTGAAACAT
GTGGTCTAATTGAAGGCCATGGTACGGGTACCAAAGCGGGTGATGCCGCAGAATTTG

FIG. 6-1

CTGGCTTGACCAAACACTTTGGCGCCGCCAGTGATGAAAAGCAATATATCGCCTTAG
GCTCAGTTAAATCGCAAATTGGTCATACTAAATCTGCGGCTGGCTCTGCGGGTATGA
TTAAGGCGGCATTAGCGCTGCATCATAAAATCTTACCTGCAACGATCCATATCGATA
AACCAAGTGAAGCCTTGGATATCAAAAACAGCCCGTTATACCTAAACAGCGAAACGC
GTCCTTGGATGCCACGTGAAGATGGTATTCCACGTCGTGCAGGTATCAGCTCATTTG
GTTTTGGCGGCACCAACTTCCATATTATTTTAGAAGAGTATCGCCCAGGTCACGATA
GCGCATATCGCTTAAACTCAGTGAGCCAAACTGTGTTGATCTCGGCAAACGACCAAC
AAGGTATTGTTGCTGAGTTAAATAACTGGCGTACTAAACTGGCTGTCGATGCTGATC
ATCAAGGGTTTGTATTTAATGAGTTAGTGACAACGTGGCCATTAAAAACCCCATCCG
TTAACCAAGCTCGTTTAGGTTTTGTTGCGCGTAATGCAAATGAAGCGATCGCGATGA
TTGATACGGCATTGAAACAATTCAATGCGAACGCAGATAAAATGACATGGTCAGTAC
CTACCGGGGTTTACTATCGTCAAGCCGGTATTGATGCAACAGGTAAAGTGGTTGCGC
TATTCTCAGGGCAAGGTTCGCAATACGTGAACATGGGTCGTGAATTAACCTGTAACT
TCCCAAGCATGATGCACAGTGCTGCGGCGATGGATAAAGAGTTCAGTGCCGCTGGTT
TAGGCCAGTTATCTGCAGTTACTTTCCCTATCCCTGTTTATACGGATGCCGAGCGTA
AGCTACAAGAAGAGCAATTACGTTTAACGCAACATGCGCAACCAGCGATTGGTAGTT
TGAGTGTTGGTCTGTTCAAAACGTTTAAGCAAGCAGGTTTTAAAGCTGATTTTGCTG
CCGGTCATAGTTTCGGTGAGTTAACCGCATTATGGGCTGCCGATGTATTGAGCGAAA
GCGATTACATGATGTTAGCGCGTAGTCGTGGTCAAGCAATGGCTGCGCCAGAGCAAC
AAGATTTTGATGCAGGTAAGATGGCCGCTGTTGTTGGTGATCCAAAGCAAGTCGCTG
TGATCATTGATACCCTTGATGATGTCTCTATTGCTAACTTCAACTCGAATAACCAAG
TTGTTATTGCTGGTACTACGGAGCAGGTTGCTGTAGCGGTTACAACCTTAGGTAATG
CTGGTTTCAAAGTTGTGCCACTGCCGGTATCTGCTGCGTTCCATACACCTTTAGTTC
GTCACGCGCAAAAACCATTTGCTAAAGCGGTTGATAGCGCTAAATTTAAAGCGCCAA
GCATTCCAGTGTTTGCTAATGGCACAGGCTTGGTGCATTCAAGCAAACCGAATGACA
TTAAGAAAAACCTGAAAAACCACATGCTGGAATCTGTTCATTTCAATCAAGAAATTG

FIG. 6-2

ACAACATCTATGCTGATGGTGGCCGCGTATTTATCGAATTTGGTCCAAAGAATGTAT
TAACTAAATTGGTTGAAAACATTCTCACTGAAAAATCTGATGTGACTGCTATCGCGG
TTAATGCTAATCCTAAACAACCTGCGGACGTACAAATGCGCCAAGCTGCGCTGCAAA
TGGCAGTGCTTGGTGTCGCATTAGACAATATTGACCCGTACGACGCCGTTAAGCGTC
CACTTGTTGCGCCGAAAGCATCACCAATGTTGATGAAGTTATCTGCAGCGTCTTATG
TTAGTCCGAAAACGAAGAAAGCGTTTGCTGATGCATTGACTGATGGCTGGACTGTTA
AGCAAGCGAAAGCTGTACCTGCTGTTGTGTCACAACCACAAGTGATTGAAAAGATCG
TTGAAGTTGAAAAGATAGTTGAACGCATTGTCGAAGTAGAGCGTATTGTCGAAGTAG
AAAAAATCGTCTACGTTAATGCTGACGGTTCGCTTATATCGCAAAATAATCAAGACG
TTAACAGCGCTGTTGTTAGCAACGTGACTAATAGCTCAGTGACTCATAGCAGTGATG
CTGACCTTGTTGCCTCTATTGAACGCAGTGTTGGTCAATTTGTTGCACACCAACAGC
AATTATTAAATGTACATGAACAGTTTATGCAAGGTCCACAAGACTACGCGAAAACAG
TGCAGAACGTACTTGCTGCGCAGACGAGCAATGAATTACCGGAAAGTTTAGACCGTA
CATTGTCTATGTATAACGAGTTCCAATCAGAAACGCTACGTGTACATGAAACGTACC
TGAACAATCAGACGAGCAACATGAACACCATGCTTACTGGTGCTGAAGCTGATGTGC
TAGCAACCCCAATAACTCAGGTAGTGAATACAGCCGTTGCCACTAGTCACAAGGTAG
TTGCTCCAGTTATTGCTAATACAGTGACGAATGTTGTATCTAGTGTCAGTAATAACG
CGGCGGTTGCAGTGCAAACTGTGGCATTAGCGCCTACGCAAGAAATCGCTCCAACAG
TCGCTACTACGCCAGCACCCGCATTGGTTGCTATCGTGGCTGAACCTGTGATTGTTG
CGCATGTTGCTACAGAAGTTGCACCAATTACACCATCAGTTACACCAGTTGTCGCAA
CTCAAGCGGCTATCGATGTAGCAACTATTAACAAAGTAATGTTAGAAGTTGTTGCTG
ATAAAACCGGTTATCCAACGGATATGCTGGAACTGAGCATGGACATGGAAGCTGACT
TAGGTATCGACTCAATCAAACGTGTTGAGATATTAGGCGCAGTACAGGAATTGATCC
CTGACTTACCTGAACTTAATCCTGAAGATCTTGCTGAGCTACGCACGCTTGGTGAGA
TTGTCGATTACATGAATTCAAAAGCCCAGGCTGTAGCTCCTACAACAGTACCTGTAA

FIG. 6-3

CAAGTGCACCTGTTTCGCCTGCATCTGCTGGTATTGATTTAGCCCACATCCAAAACG
TAATGTTAGAAGTGGTTGCAGACAAAACCGGTTACCCAACAGACATGCTAGAACTGA
GCATGGATATGGAAGCTGACTTAGGTATTGATTCAATCAAGCGTGTGGAAATCTTAG
GTGCAGTACAGGAGATCATAACTGATTTACCTGAGCTAAACCCTGAAGATCTTGCTG
AATTACGCACCCTAGGTGAAATCGTTAGTTACATGCAAAGCAAAGCGCCAGTCGCTG
AAAGTGCGCCAGTGGCGACGGCTCCTGTAGCAACAAGCTCAGCACCGTCTATCGATT
TGAACCACATTCAAACAGTGATGATGGATGTAGTTGCAGATAAGACTGGTTATCCAA
CTGACATGCTAGAACTTGGCATGGACATGGAAGCTGATTTAGGTATCGATTCAATCA
AACGTGTGGAAATATTAGGCGCAGTGCAGGAGATCATCACTGATTTACCTGAGCTAA
ACCCAGAAGACCTCGCTGAATTACGCACGCTAGGTGAAATCGTTAGTTACATGCAAA
GCAAAGCGCCAGTCGCTGAGAGTGCGCCAGTAGCGACGGCTTCTGTAGCAACAAGCT
CTGCACCGTCTATCGATTTAAACCATATCCAAACAGTGATGATGGAAGTGGTTGCAG
ACAAAACCGGTTATCCAGTAGACATGTTAGAACTTGCTATGGACATGGAAGCTGACC
TAGGTATCGATTCAATCAAGCGTGTAGAAATTTTAGGTGCGGTACAGGAAATCATTA
CTGACTTACCTGAGCTTAACCCTGAAGATCTTGCTGAACTACGTACATTAGGTGAAA
TCGTTAGTTACATGCAAAGCAAAGCGCCCGTAGCTGAAGCGCCTGCAGTACCTGTTG
CAGTAGAAAGTGCACCTACTAGTGTAACAAGCTCAGCACCGTCTATCGATTTAGACC
ACATCCAAAATGTAATGATGGATGTTGTTGCTGATAAGACTGGTTATCCTGCCAATA
TGCTTGAATTAGCAATGGACATGGAAGCCGACCTTGGTATTGATTCAATCAAGCGTG
TTGAAATTCTAGGCGCGGTACAGGAGATCATTACTGATTTACCTGAACTAAACCCAG
AAGACTTAGCTGAACTACGTACGTTAGAAGAAATTGTAACCTACATGCAAAGCAAGG
CGAGTGGTGTTACTGTAAATGTAGTGGCTAGCCCTGAAAATAATGCTGTATCAGATG
CATTTATGCAAAGCAATGTGGCGACTATCACAGCGGCCGCAGAACATAAGGCGGAAT
TTAAACCGGCGCCGAGCGCAACCGTTGCTATCTCTCGTCTAAGCTCTATCAGTAAAA
TAAGCCAAGATTGTAAAGGTGCTAACGCCTTAATCGTAGCTGATGGCACTGATAATG
CTGTGTTACTTGCAGACCACCTATTGCAAACTGGCTGGAATGTAACTGCATTGCAAC
CAACTTGGGTAGCTGTAACAACGACGAAAGCATTTAATAAGTCAGTGAACCTGGTGA

FIG. 6-4

CTTTAAATGGCGTTGATGAAACTGAAATCAACAACATTATTACTGCTAACGCACAAT
TGGATGCAGTTATCTATCTGCACGCAAGTAGCGAAATTAATGCTATCGAATACCCAC
AAGCATCTAAGCAAGGCCTGATGTTAGCCTTCTTATTAGCGAAATTGAGTAAAGTAA
CTCAAGCCGCTAAAGTGCGTGGCGCCTTTATGATTGTTACTCAGCAGGGTGGTTCAT
TAGGTTTTGATGATATCGATTCTGCTACAAGTCATGATGTGAAAACAGACCTAGTAC
AAAGCGGCTTAAACGGTTTAGTTAAGACACTGTCTCACGAGTGGGATAACGTATTCT
GTCGTGCGGTTGATATTGCTTCGTCATTAACGGCTGAACAAGTTGCAAGCCTTGTTA
GTGATGAACTACTTGATGCTAACACTGTATTAACAGAAGTGGGTTATCAACAAGCTG
GTAAAGGCCTTGAACGTATCACGTTAACTGGTGTGGCTACTGACAGCTATGCATTAA
CAGCTGGCAATAACATCGATGCTAACTCGGTATTTTTAGTGAGTGGTGGCGCAAAAG
GTGTAACTGCACATTGTGTTGCTCGTATAGCTAAAGAATATCAGTCTAAGTTCATCT
TATTGGGACGTTCAACGTTCTCAAGTGACGAACCGAGCTGGGCAAGTGGTATTACTG
ATGAAGCGGCGTTAAAGAAAGCAGCGATGCAGTCTTTGATTACAGCAGGTGATAAAC
CAACACCCGTTAAGATCGTACAGCTAATCAAACCAATCCAAGCTAATCGTGAAATTG
CGCAAACCTTGTCTGCAATTACCGCTGCTGGTGGCCAAGCTGAATATGTTTCTGCAG
ATGTAACTAATGCAGCAAGCGTACAAATGGCAGTCGCTCCAGCTATCGCTAAGTTCG
GTGCAATCACTGGCATCATTCATGGCGCGGGTGTGTTAGCTGACCAATTCATTGAGC
AAAAAACACTGAGTGATTTTGAGTCTGTTTACAGCACTAAAATTGACGGTTTGTTAT
CGCTACTATCAGTCACTGAAGCAAGCAACATCAAGCAATTGGTATTGTTCTCGTCAG
CGGCTGGTTTCTACGGTAACCCCGGCCAGTCTGATTACTCGATTGCCAATGAGATCT
TAAATAAAACCGCATACCGCTTTAAATCATTGCACCCACAAGCTCAAGTATTGAGCT
TTAACTGGGGTCCTTGGGACGGTGGCATGGTAACGCCTGAGCTTAAACGTATGTTTG
ACCAACGTGGTGTTTACATTATTCCACTTGATGCAGGTGCACAGTTATTGCTGAATG
AACTAGCCGCTAATGATAACCGTTGTCCACAAATCCTCGTGGGTAATGACTTATCTA
AAGATGCTAGCTCTGATCAAAAGTCTGATGAAAAGAGTACTGCTGTAAAAAAGCCAC
AAGTTAGTCGTTTATCAGATGCTTTAGTAACTAAAAGTATCAAAGCGACTAACAGTA

FIG. 6-5

GCTCTTTATCAAACAAGACTAGTGCTTTATCAGACAGTAGTGCTTTTCAGGTTAACG
AAAACCACTTTTTAGCTGACCACATGATCAAAGGCAATCAGGTATTACCAACGGTAT
GCGCGATTGCTTGGATGAGTGATGCAGCAAAAGCGACTTATAGTAACCGAGACTGTG
CATTGAAGTATGTCGGTTTCGAAGACTATAAATTGTTTAAAGGTGTGGTTTTTGATG
GCAATGAGGCGGCGGATTACCAAATCCAATTGTCGCCTGTGACAAGGGCGTCAGAAC
AGGATTCTGAAGTCCGTATTGCCGCAAAGATCTTTAGCCTGAAAAGTGACGGTAAAC
CTGTGTTTCATTATGCAGCGACAATATTGTTAGCAACTCAGCCACTTAATGCTGTGA
AGGTAGAACTTCCGACATTGACAGAAAGTGTTGATAGCAACAATAAAGTAACTGATG
AAGCACAAGCGTTATACAGCAATGGCACCTTGTTCCACGGTGAAAGTCTGCAGGGCA
TTAAGCAGATATTAAGTTGTGACGACAAGGGCCTGCTATTGGCTTGTCAGATAACCG
ATGTTGCAACAGCTAAGCAGGGATCCTTCCCGTTAGCTGACAACAATATCTTTGCCA
ATGATTTGGTTTATCAGGCTATGTTGGTCTGGGTGCGCAAACAATTTGGTTTAGGTA
GCTTACCTTCGGTGACAACGGCTTGGACTGTGTATCGTGAAGTGGTTGTAGATGAAG
TATTTTATCTGCAACTTAATGTTGTTGAGCATGATCTATTGGGTTCACGCGGCAGTA
AAGCCCGTTGTGATATTCAATTGATTGCTGCTGATATGCAATTACTTGCCGAAGTGA
AATCAGCGCAAGTCAGTGTCAGTGACATTTTGAACGATATGTCATGATCGAGTAAAT
AATAACGATAGGCGTCATGGTGAGCATGGCGTCTGCTTTCTTCATTTTTTAACATTA
ACAATATTAATAGCTAAACGCGGTTGCTTTAAACCAAGTAAACAAGTGCTTTTAGCT
ATTACTATTCCAAACAGGATATTAAAGAGAATATGACGGAATTAGCTGTTATTGGTA
TGGATGCTAAATTTAGCGGACAAGACAATATTGACCGTGTGGAACGCGCTTTCTATG
AAGGTGCTTATGTAGGTAATGTTAGCCGCGTTAGTACCGAATCTAATGTTATTAGCA
ATGGCGAAGAACAAGTTATTACTGCCATGACAGTTCTTAACTCTGTCAGTCTACTAG
CGCAAACGAATCAGTTAAATATAGCTGATATCGCGGTGTTGCTGATTGCTGATGTAA
AAAGTGCTGATGATCAGCTTGTAGTCCAAATTGCATCAGCAATTGAAAAACAGTGTG
CGAGTTGTGTTGTTATTGCTGATTTAGGCCAAGCATTAAATCAAGTAGCTGATTTAG

FIG. 6-6

TTAATAACCAAGACTGTCCTGTGGCTGTAATTGGCATGAATAACTCGGTTAATTTAT
CTCGTCATGATCTTGAATCTGTAACTGCAACAATCAGCTTTGATGAAACCTTCAATG
GTTATAACAATGTAGCTGGGTTCGCGAGTTTACTTATCGCTTCAACTGCGTTTGCCA
ATGCTAAGCAATGTTATATATACGCCAACATTAAGGGCTTCGCTCAATCGGGCGTAA
ATGCTCAATTTAACGTTGGAAACATTAGCGATACTGCAAAGACCGCATTGCAGCAAG
CTAGCATAACTGCAGAGCAGGTTGGTTTGTTAGAAGTGTCAGCAGTCGCTGATTCGG
CAATCGCATTGTCTGAAAGCCAAGGTTTAATGTCTGCTTATCATCATACGCAAACTT
TGCATACTGCATTAAGCAGTGCCCGTAGTGTGACTGGTGAAGGCGGGTGTTTTTCAC
AGGTCGCAGGTTTATTGAAATGTGTAATTGGTTTACATCAACGTTATATTCCGGCGA
TTAAAGATTGGCAACAACCGAGTGACAATCAAATGTCACGGTGGCGGAATTCACCAT
TCTATATGCCTGTAGATGCTCGACCTTGGTTCCCACATGCTGATGGCTCTGCACACA
TTGCCGCTTATAGTTGTGTGACTGCTGACAGCTATTGTCATATTCTTTTACAAGAAA
ACGTCTTACAAGAACTTGTTTTGAAAGAAACAGTCTTGCAAGATAATGACTTAACTG
AAAGCAAGCTTCAGACTCTTGAACAAAACAATCCAGTAGCTGATCTGCGCACTAATG
GTTACTTTGCATCGAGCGAGTTAGCATTAATCATAGTACAAGGTAATGACGAAGCAC
AATTACGCTGTGAATTAGAAACTATTACAGGGCAGTTAAGTACTACTGGCATAAGTA
CTATCAGTATTAAACAGATCGCAGCAGACTGTTATGCCCGTAATGATACTAACAAAG
CCTATAGCGCAGTGCTTATTGCCGAGACTGCTGAAGAGTTAAGCAAAGAAATAACCT
TGGCGTTTGCTGGTATCGCTAGCGTGTTTAATGAAGATGCTAAAGAATGGAAAACCC
CGAAGGGCAGTTATTTTACCGCGCAGCCTGCAAATAAACAGGCTGCTAACAGCACAC
AGAATGGTGTCACCTTCATGTACCCAGGTATTGGTGCTACATATGTTGGTTTAGGGC
GTGATCTATTTCATCTATTCCCACAGATTTATCAGCCTGTAGCGGCTTTAGCCGATG
ACATTGGCGAAAGTCTAAAAGATACTTTACTTAATCCACGCAGTATTAGTCGTCATA
GCTTTAAAGAACTCAAGCAGTTGGATCTGGACCTGCGCGGTAACTTAGCCAATATCG
CTGAAGCCGGTGTGGGTTTTGCTTGTGTGTTTACCAAGGTATTTGAAGAAGTCTTTG
CCGTTAAAGCTGACTTTGCTACAGGTTATAGCATGGGTGAAGTAAGCATGTATGCAG
CACTAGGCTGCTGGCAGCAACCGGGATTGATGAGTGCTCGCCTTGCACAATCGAATA

FIG. 6-7

CCTTTAATCATCAACTTTGCGGCGAGTTAAGAACACTACGTCAGCATTGGGGCATGG
ATGATGTAGCTAACGGTACGTTCGAGCAGATCTGGGAAACCTATACCATTAAGGCAA
CGATTGAACAGGTCGAAATTGCCTCTGCAGATGAAGATCGTGTGTATTGCACCATTA
TCAATACACCTGATAGCTTGTTGTTAGCCGGTTATCCAGAAGCCTGTCAGCGAGTCA
TTAAGAATTTAGGTGTGCGTGCAATGGCATTGAATATGGCGAACGCAATTCACAGCG
CGCCAGCTTATGCCGAATACGATCATATGGTTGAGCTATACCATATGGATGTTACTC
CACGTATTAATACCAAGATGTATTCAAGCTCATGTTATTTACCGATTCCACAACGCA
GCAAAGCGATTTCCCACAGTATTGCTAAATGTTTGTGTGATGTGGTGGATTTCCCAC
GTTTGGTTAATACCTTACATGACAAAGGTGCGCGGGTATTCATTGAAATGGGTCCAG
GTCGTTCGTTATGTAGCTGGGTAGATAAGATCTTAGTTAATGGCGATGGCGATAATA
AAAAGCAAAGCCAACATGTATCTGTTCCTGTGAATGCCAAAGGCACCAGTGATGAAC
TTACTTATATTCGTGCGATTGCTAAGTTAATTAGTCATGGCGTGAATTTGAATTTAG
ATAGCTTGTTTAACGGGTCAATCCTGGTTAAAGCAGGCCATATAGCAAACACGAACA
AATAGTCAACATCGATATCTAGCGCTGGTGAGTTATACCTCATTAGTTGAAATATGG
ATTTAAAGAGAGTAATTATGGAAAATATTGCAGTAGTAGGTATTGCTAATTTGTTCC
CGGGCTCACAAGCACCGGATCAATTTTGGCAGCAATTGCTTGAACAACAAGATTGCC
GCAGTAAGGCGACCGCTGTTCAAATGGGCGTTGATCCTGCTAAATATACCGCCAACA
AAGGTGACACAGATAAATTTTACTGTGTGCACGGCGGTTACATCAGTGATTTCAATT
TTGATGCTTCAGGTTATCAACTCGATAATGATTATTTAGCCGGTTTAGATGACCTTA
ATCAATGGGGGCTTTATGTTACGAAACAAGCCCTTACCGATGCGGGTTATTGGGGCA
GTACTGCACTAGAAAACTGTGGTGTGATTTTAGGTAATTTGTCATTCCCAACTAAAT
CATCTAATCAGCTGTTTATGCCTTTGTATCATCAAGTTGTTGATAATGCCTTAAAGG
CGGTATTACATCCTGATTTTCAATTAACGCATTACACAGCACCGAAAAAAACACATG
CTGACAATGCATTAGTAGCAGGTTATCCAGCTGCATTGATCGCGCAAGCGGCGGGTC
TTGGTGGTTCACATTTTGCACTGGATGCGGCTTGTGCTTCATCTTGTTATAGCGTTA
AGTTAGCGTGTGATTACCTGCATACGGGTAAAGCCAACATGATGCTTGCTGGTGCGG

FIG. 6-8

TATCTGCAGCAGATCCTATGTTCGTAAATATGGGTTTCTCGATATTCCAAGCTTACC
CAGCTAACAATGTACATGCCCCGTTTGACCAAAATTCACAAGGTCTATTTGCCGGTG
AAGGCGCGGGCATGATGGTATTGAAACGTCAAAGTGATGCAGTACGTGATGGTGATC
ATATTTACGCCATTATTAAAGGCGGCGCATTATCGAATGACGGTAAAGGCGAGTTTG
TATTAAGCCCGAACACCAAGGGCCAAGTATTAGTATATGAACGTGCTTATGCCGATG
CAGATGTTGACCCGAGTACAGTTGACTATATTGAATGTCATGCAACGGGCACACCTA
AGGGTGACAATGTTGAATTGCGTTCGATGGAAACCTTTTTCAGTCGCGTAAATAACA
AACCATTACTGGGCTCGGTTAAATCTAACCTTGGTCATTTGTTAACTGCCGCTGGTA
TGCCTGGCATGACCAAAGCTATGTTAGCGCTAGGTAAAGGTCTTATTCCTGCAACGA
TTAACTTAAAGCAACCACTGCAATCTAAAAACGGTTACTTTACTGGCGAGCAAATGC
CAACGACGACTGTGTCTTGGCCAACAACTCCGGGTGCCAAGGCAGATAAACCGCGTA
CCGCAGGTGTGAGCGTATTTGGTTTTGGTGGCAGCAACGCCCATTTGGTATTACAAC
AGCCAACGCAAACACTCGAGACTAATTTTAGTGTTGCTAAACCACGTGAGCCTTTGG
CTATTATTGGTATGGACAGCCATTTTGGTAGTGCCAGTAATTTAGCGCAGTTCAAAA
CCTTATTAAATAATAATCAAAATACCTTCCGTGAATTACCAGAACAACGCTGGAAAG
GCATGGAAAGTAACGCTAACGTCATGCAGTCGTTACAATTACGCAAAGCGCCTAAAG
GCAGTTACGTTGAACAGCTAGATATTGATTTCTTGCGTTTTAAAGTACCGCCTAATG
AAAAAGATTGCTTGATCCCGCAACAGTTAATGATGATGCAAGTGGCAGACAATGCTG
CGAAAGACGGAGGTCTAGTTGAAGGTCGTAATGTTGCGGTATTAGTAGCGATGGGCA
TGGAACTGGAATTACATCAGTATCGTGGTCGCGTTAATCTAACCACCCAAATTGAAG
ACAGCTTATTACAGCAAGGTATTAACCTGACTGTTGAGCAACGTGAAGAACTGACCA
ATATTGCTAAAGACGGTGTTGCCTCGGCTGCACAGCTAAATCAGTATACGAGTTTCA
TTGGTAATATTATGGCGTCACGTATTTCGGCGTTATGGGATTTTTCTGGTCCTGCTA
TTACCGTATCGGCTGAAGAAAACTCTGTTTATCGTTGTGTTGAATTAGCTGAAAATC
TATTTCAAACCAGTGATGTTGAAGCCGTTATTATTGCTGCTGTTGATTTGTCTGGTT
CAATTGAAAACATTACTTTACGTCAGCACTACGGTCCAGTTAATGAAAAGGGATCTG

FIG. 6-9

TAAGTGAATGTGGTCCGGTTAATGAAAGCAGTTCAGTAACCAACAATATTCTTGATC
AGCAACAATGGCTGGTGGGTGAAGGCGCAGCGGCTATTGTCGTTAAACCGTCATCGC
AAGTCACTGCTGAGCAAGTTTATGCGCGTATTGATGCGGTGAGTTTTGCCCCTGGTA
GCAATGCGAAAGCAATTACGATTGCAGCGGATAAAGCATTAACACTTGCTGGTATCA
GTGCTGCTGATGTAGCTAGTGTTGAAGCACATGCAAGTGGTTTTAGTGCCGAAAATA
ATGCTGAAAAAACCGCGTTACCGACTTTATACCCAAGCGCAAGTATCAGTTCGGTGA
AAGCCAATATTGGTCATACGTTTAATGCCTCGGGTATGGCGAGTATTATTAAAACGG
CGCTGCTGTTAGATCAGAATACGAGTCAAGATCAGAAAAGCAAACATATTGCTATTA
ACGGTCTAGGTCGTGATAACAGCTGCGCGCATCTTATCTTATCGAGTTCAGCGCAAG
CGCATCAAGTTGCACCAGCGCCTGTATCTGGTATGGCCAAGCAACGCCCACAGTTAG
TTAAAACCATCAAACTCGGTGGTCAGTTAATTAGCAACGCGATTGTTAACAGTGCGA
GTTCATCTTTACACGCTATTAAAGCGCAGTTTGCCGGTAAGCACTTAAACAAAGTTA
ACCAGCCAGTGATGATGGATAACCTGAAGCCCCAAGGTATTAGCGCTCATGCAACCA
ATGAGTATGTGGTGACTGGAGCTGCTAACACTCAAGCTTCTAACATTCAAGCATCTC
ATGTTCAAGCGTCAAGTCATGCACAAGAGATAGCACCAAACCAAGTTCAAAATATGC
AAGCTACAGCAGCCGCTGTAAGTTCACCCCTTTCTCAACATCAACACACAGCGCAGC
CCGTAGCGGCACCGAGCGTTGTTGGAGTGACTGTGAAACATAAAGCAAGTAACCAAA
TTCATCAGCAAGCGTCTACGCATAAAGCATTTTTAGAAAGTCGTTTAGCTGCACAGA
AAAACCTATCGCAACTTGTTGAATTGCAAACCAAGCTGTCAATCCAAACTGGTAGTG
ACAATACATCTAACAATACTGCGTCAACAAGCAATACAGTGCTAACAAATCCTGTAT
CAGCAACGCCATTAACACTTGTGTCTAATGCGCCTGTAGTAGCGACAAACCTAACCA
GTACAGAAGCAAAAGCGCAAGCAGCTGCTACACAAGCTGGTTTTCAGATAAAAGGAC
CTGTTGGTTACAACTATCCACCGCTGCAGTTAATTGAACGTTATAATAAACCAGAAA
ACGTGATTTACGATCAAGCTGATTTGGTTGAATTCGCTGAAGGTGATATTGGTAAGG
TATTTGGTGCTGAATACAATATTATTGATGGCTATTCGCGTCGTGTACGTCTGCCAA
CCTCAGATTACTTGTTAGTAACACGTGTTACTGAACTTGATGCCAAGGTGCATGAAT

FIG. 6-10

ACAAGAAATCATACATGTGTACTGAATATGATGTGCCTGTTGATGCACCGTTCTTAA
TTGATGGTCAGATCCCTTGGTCTGTTGCCGTCGAATCAGGCCAGTGTGATTTGATGT
TGATTTCATATATCGGTATTGATTTCCAAGCGAAAGGCGAACGTGTTTACCGTTTAC
TTGATTGTGAATTAACTTTCCTTGAAGAGATGGCTTTTGGTGGCGATACTTTACGTT
ACGAGATCCACATTGATTCGTATGCACGTAACGGCGAGCAATTATTATTCTTCTTCC
ATTACGATTGTTACGTAGGGGATAAGAAGGTACTTATCATGCGTAATGGTTGTGCTG
GTTTCTTTACTGACGAAGAACTTTCTGATGGTAAAGGCGTTATTCATAACGACAAAG
ACAAAGCTGAGTTTAGCAATGCTGTTAAATCATCATTCACGCCGTTATTACAACATA
ACCGTGGTCAATACGATTATAACGACATGATGAAGTTGGTTAATGGTGATGTTGCCA
GTTGTTTTGGTCCGCAATATGATCAAGGTGGCCGTAATCCATCATTGAAATTCTCGT
CTGAGAAGTTCTTGATGATTGAACGTATTACCAAGATAGACCCAACCGGTGGTCATT
GGGGACTAGGCCTGTTAGAAGGTCAGAAAGATTTAGACCCTGAGCATTGGTATTTCC
CTTGTCACTTTAAAGGTGATCAAGTAATGGCTGGTTCGTTGATGTCGGAAGGTTGTG
GCCAAATGGCGATGTTCTTCATGCTGTCTCTTGGTATGCATACCAATGTGAACAACG
CTCGTTTCCAACCACTACCAGGTGAATCACAAACGGTACGTTGTCGTGGGCAAGTAC
TGCCACAGCGCAATACCTTAACTTACCGTATGGAAGTTACTGCGATGGGTATGCATC
CACAGCCATTCATGAAAGCTAATATTGATATTTTGCTTGACGGTAAAGTGGTTGTTG
ATTTCAAAAACTTGAGCGTGATGATCAGCGAACAAGATGAGCATTCAGATTACCCTG
TAACACTGCCGAGTAATGTGGCGCTTAAAGCGATTACTGCACCTGTTGCGTCAGTAG
CACCAGCATCTTCACCCGCTAACAGCGCGGATCTAGACGAACGTGGTGTTGAACCGT
TTAAGTTTCCTGAACGTCCGTTAATGCGTGTTGAGTCAGACTTGTCTGCACCGAAAA
GCAAAGGTGTGACACCGATTAAGCATTTTGAAGCGCCTGCTGTTGCTGGTCATCATA
GAGTGCCTAACCAAGCACCGTTTACACCTTGGCATATGTTTGAGTTTGCGACGGGTA
ATATTTCTAACTGTTTCGGTCCTGATTTTGATGTTTATGAAGGTCGTATTCCACCTC
GTACACCTTGTGGCGATTTACAAGTTGTTACTCAGGTTGTAGAAGTGCAGGGCGAAC
GTCTTGATCTTAAAAATCCATCAAGCTGTGTAGCTGAATACTATGTACCGGAAGACG

FIG. 6-11

CTTGGTACTTTACTAAAAACAGCCATGAAAACTGGATGCCTTATTCATTAATCATGG
AAATTGCATTGCAACCAAATGGCTTTATTTCTGGTTACATGGGCACGACGCTTAAAT
ACCCTGAAAAAGATCTGTTCTTCCGTAACCTTGATGGTAGCGGCACGTTATTAAAGC
AGATTGATTTACGCGGCAAGACCATTGTGAATAAATCAGTCTTGGTTAGTACGGCTA
TTGCTGGTGGCGCGATTATTCAAAGTTTCACGTTTGATATGTCTGTAGATGGCGAGC
TATTTTATACTGGTAAAGCTGTATTTGGTTACTTTAGTGGTGAATCACTGACTAACC
AACTGGGCATTGATAACGGTAAAACGACTAATGCGTGGTTTGTTGATAACAATACCC
CCGCAGCGAATATTGATGTGTTTGATTTAACTAATCAGTCATTGGCTCTGTATAAAG
CGCCTGTGGATAAACCGCATTATAAATTGGCTGGTGGTCAGATGAACTTTATCGATA
CAGTGTCAGTGGTTGAAGGCGGTGGTAAAGCGGGCGTGGCTTATGTTTATGGCGAAC
GTACGATTGATGCTGATGATTGGTTCTTCCGTTATCACTTCCACCAAGATCCGGTGA
TGCCAGGTTCATTAGGTGTTGAAGCTATTATTGAGTTGATGCAGACCTATGCGCTTA
AAAATGATTTGGGTGGCAAGTTTGCTAACCCACGTTTCATTGCGCCGATGACGCAAG
TTGATTGGAAATACCGTGGGCAAATTACGCCGCTGAATAAACAGATGTCACTGGACG
TGCATATCACTGAGATCGTGAATGACGCTGGTGAAGTGCGAATCGTTGGTGATGCGA
ATCTGTCTAAAGATGGTCTGCGTATTTATGAAGTTAAAAACATCGTTTTAAGTATTG
TTGAAGCGTAAAGGGTCAAGTGTAACGTGCTTAAGCGCCGCATTGGTTAAAGACGCT
TTGCACGCCGTGAATCCGTCCATGGAGGCTTGGGGTTGGCATCCATGCCAACAACAG
CAAGCTTACTTTAATCAATACGGCTTGGTGTCCATTTAGACGCCTCGAACTTAGTAG
TTAATAGACAAAATAATTTAGCTGTGGAATGAATATAGTAAGTAATCATTCGGCAGC
TACAAAAAAGGAATTAAGAATGTCGAGTTTAGGTTTTAACAATAACAACGCAATTAA
CTGGGCTTGGAAAGTAGATCCAGCGTCAGTTCATACACAAGATGCAGAAATTAAAGC
AGCTTTAATGGATCTAACTAAACCTCTCTATGTGGCGAATAATTCAGGCGTAACTGG
TATAGCTAATCATACGTCAGTAGCAGGTGCGATCAGCAATAACATCGATGTTGATGT
ATTGGCGTTTGCGCAAAAGTTAAACCCAGAAGATCTGGGTGATGATGCTTACAAGAA
ACAGCACGGCGTTAAATATGCTTATCATGGCGGTGCGATGGCAAATGGTATTGCCTC

FIG. 6-12

GGTTGAATTGGTTGTTGCGTTAGGTAAAGCAGGGCTGTTATGTTCATTTGGTGCTGC
AGGTCTAGTGCCTGATGCGGTTGAAGATGCAATTCGTCGTATTCAAGCTGAATTACC
AAATGGCCCTTATGCGGTTAACTTGATCCATGCACCAGCAGAAGAAGCATTAGAGCG
TGGCGCGGTTGAACGTTTCCTAAAACTTGGCGTCAAGACGGTAGAGGCTTCAGCTTA
CCTTGGTTTAACTGAACACATTGTTTGGTATCGTGCTGCTGGTCTAACTAAAAACGC
AGATGGCAGTGTTAATATCGGTAACAAGGTTATCGCTAAAGTATCGCGTACCGAAGT
TGGTCGCCGCTTTATGGAACCTGCACCGCAAAAATTACTGGATAAGTTATTAGAACA
AAATAAGATCACCCCTGAACAAGCTGCTTTAGCGTTGCTTGTACCTATGGCTGATGA
TATTACTGGGGAAGCGGATTCTGGTGGTCATACAGATAACCGTCCGTTTTTAACATT
ATTACCGACGATTATTGGTCTGCGTGATGAAGTGCAAGCGAAGTATAACTTCTCTCC
TGCATTACGTGTTGGTGCTGGTGGTGGTATCGGAACGCCTGAAGCAGCACTCGCTGC
ATTTAACATGGGCGCGGCTTATATCGTTCTGGGTTCTGTGAATCAGGCGTGTGTTGA
AGCGGGTGCATCTGAATATACTCGTAAACTGTTATCGACAGTTGAAATGGCTGATGT
GACTATGGCACCTGCTGCAGATATGTTTGAAATGGGTGTGAAGCTGCAAGTATTAAA
ACGCGGTTCTATGTTCGCGATGCGTGCGAAGAAACTGTATGACTTGTATGTGGCTTA
TGACTCGATTGAAGATATCCCAGCTGCTGAACGTGAGAAGATTGAAAAACAAATCTT
CCGTGCAAACCTAGACGAGATTTGGGATGGCACTATCGCTTTCTTTACTGAACGCGA
TCCAGAAATGCTAGCCCGTGCAACGAGTAGTCCTAAACGTAAAATGGCACTTATCTT
CCGTTGGTATCTTGGCCTTTCTTCACGCTGGTCAAACACAGGCGAGAAGGGACGTGA
AATGGATTATCAGATTTGGGCAGGCCCAAGTTTAGGTGCATTCAACAGCTGGGTGAA
AGGTTCTTACCTTGAAGACTATACCCGCCGTGGCGCTGTAGATGTTGCTTTGCATAT
GCTTAAAGGTGCTGCGTATTTACAACGTGTAAACCAGTTGAAATTGCAAGGTGTTAG
CTTAAGTACAGAATTGGCAAGTTATCGTACGAGTGATTAATGTTACTTGATGATATG
TGAATTAATTAAAGCGCCTGAGGGCGCTTTTTTTGGTTTTTAACTCAGGTGTTGTAA
CTCGAAATTGCCCCTTTC
*
19227

FIG. 6-13

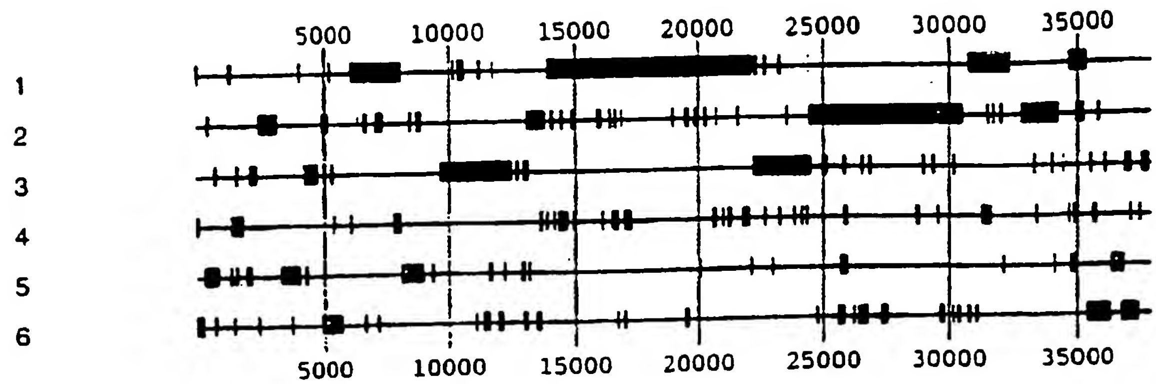
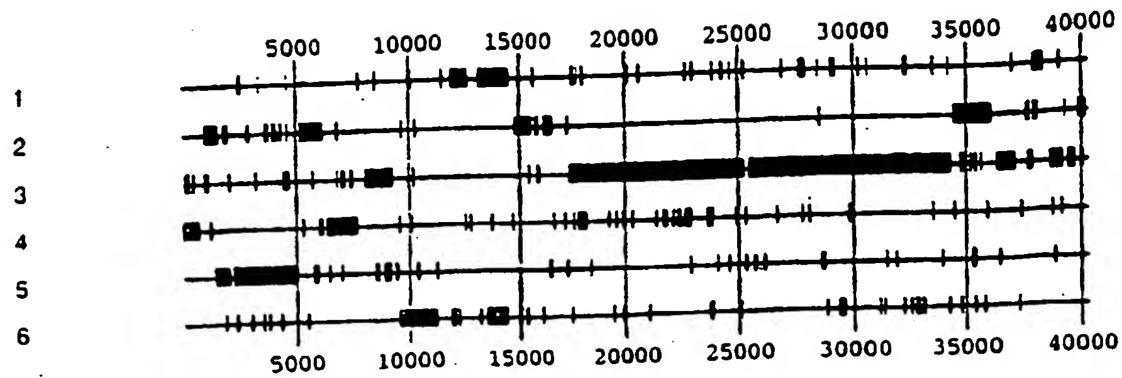

5000
10000
15000
20000
25000
30000
35000
1
2
3
4
5
6
5000
10000
15000
20000
25000
30000
35000

FIG. 7A



5000
10000
15000
20000
25000
30000
35000
40000
1
2
3
4
5
6
5000
10000
15000
20000
25000
30000
35000
40000

FIG. 7B

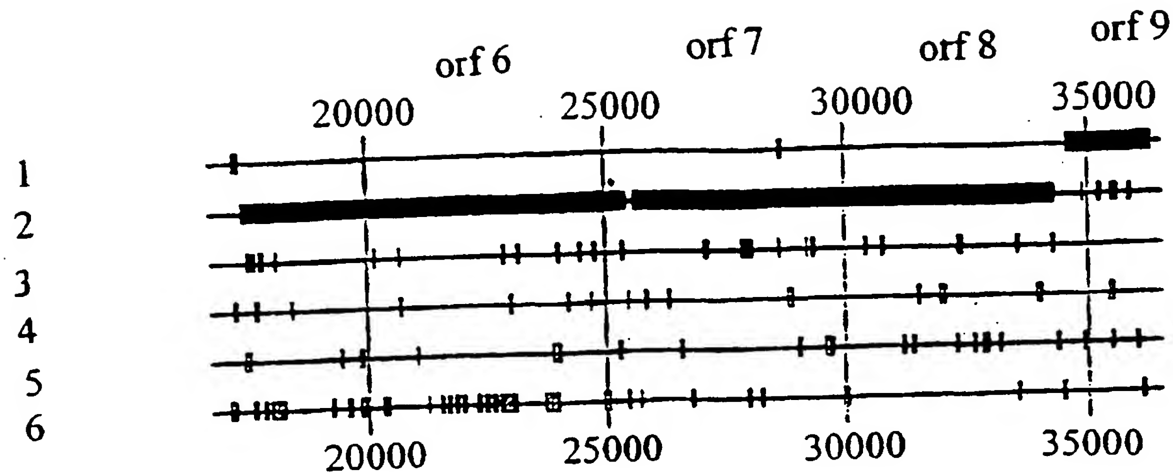

orf 6
orf 7
orf 8
orf 9
20000
25000
30000
35000
1
2
3
4
5
6
20000
25000
30000
35000

FIG. 8

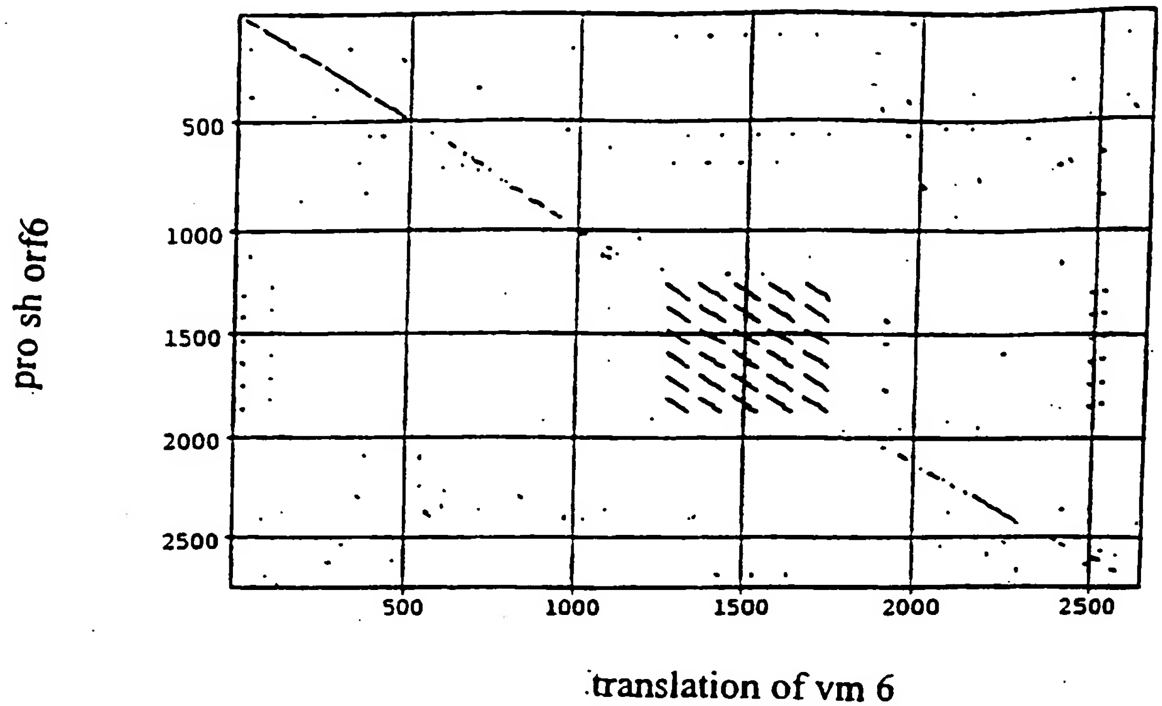

pro sh orf6
500
1000
1500
2000
2500
500
1000
1500
2000
2500
translation of vm 6

FIG. 9

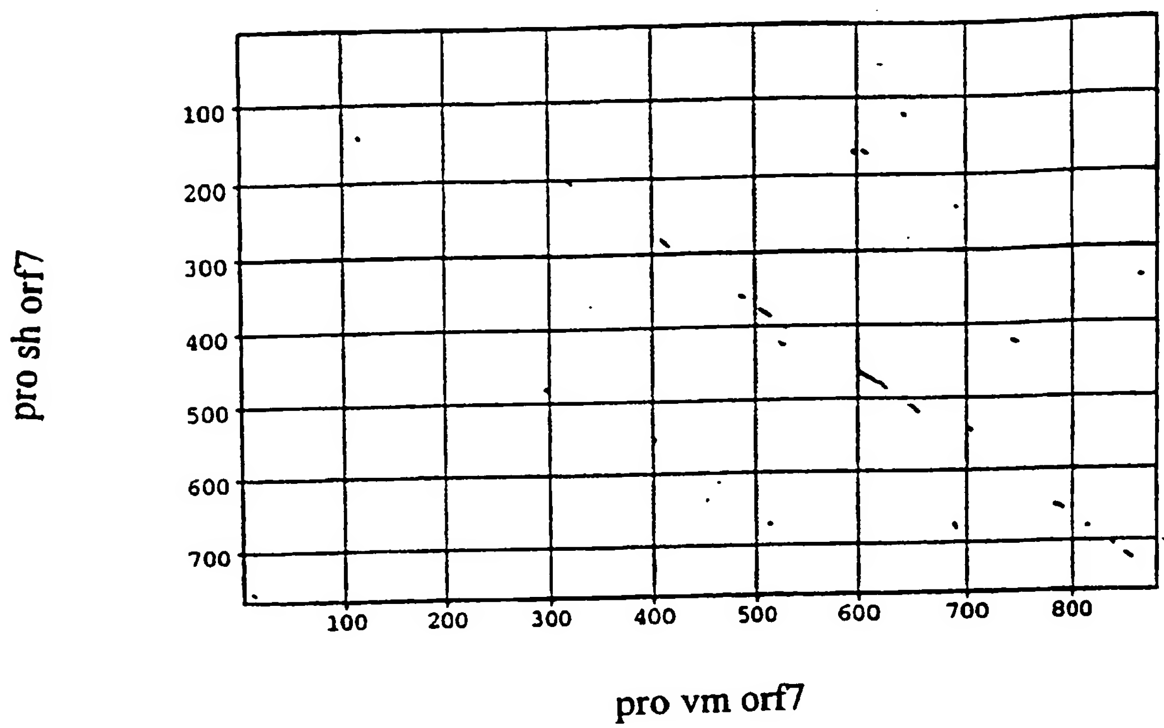

100
200
300
400
500
600
700
100
200
300
400
500
600
700
800
pro sh orf7
pro vm orf7

FIG. 10

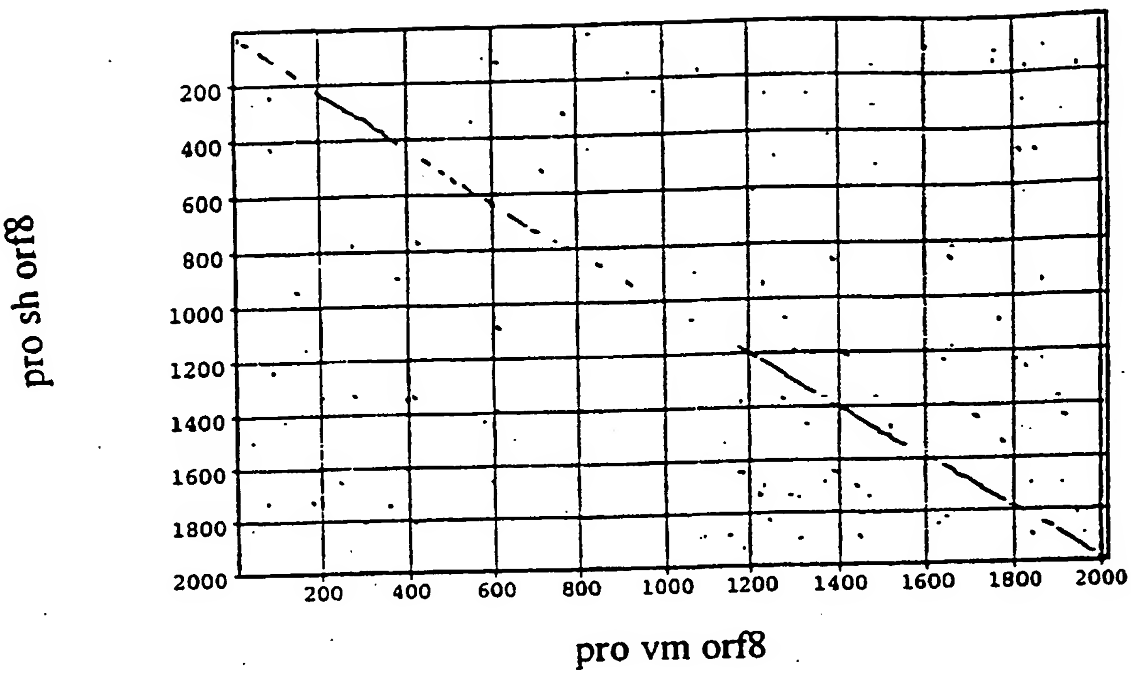

200
400
600
800
1000
1200
1400
1600
1800
2000
pro sh orf8
200
400
600
800
1000
1200
1400
1600
1800
2000
pro vm orf8

FIG. 11

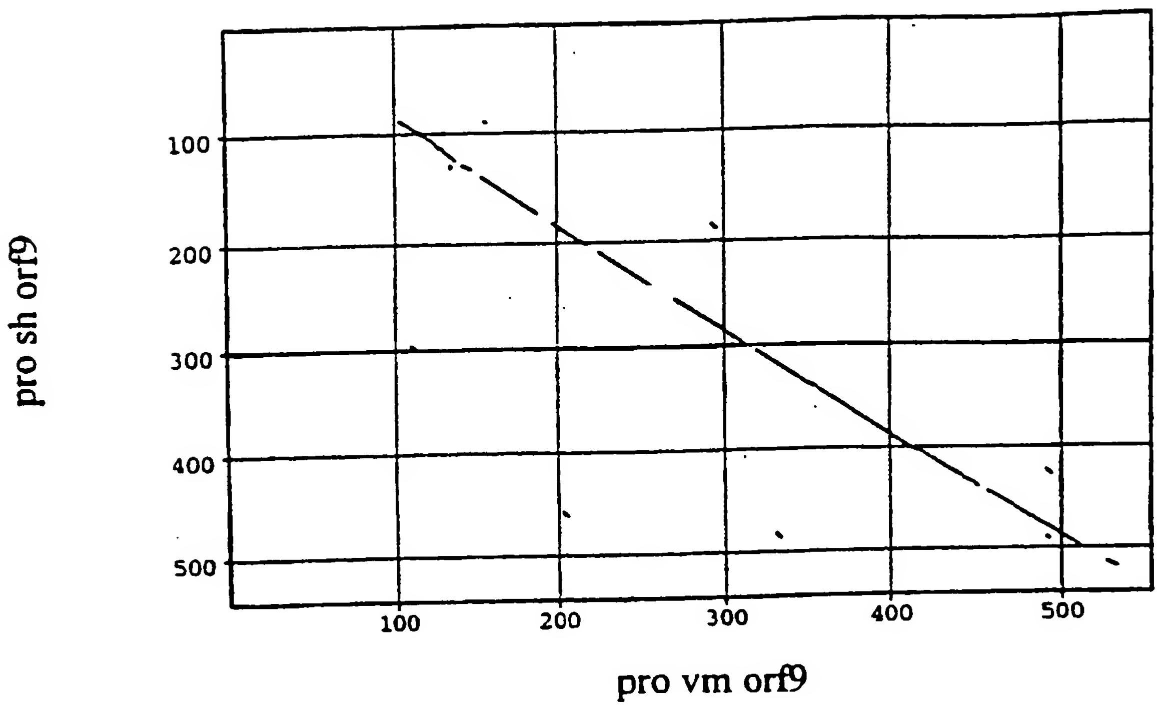
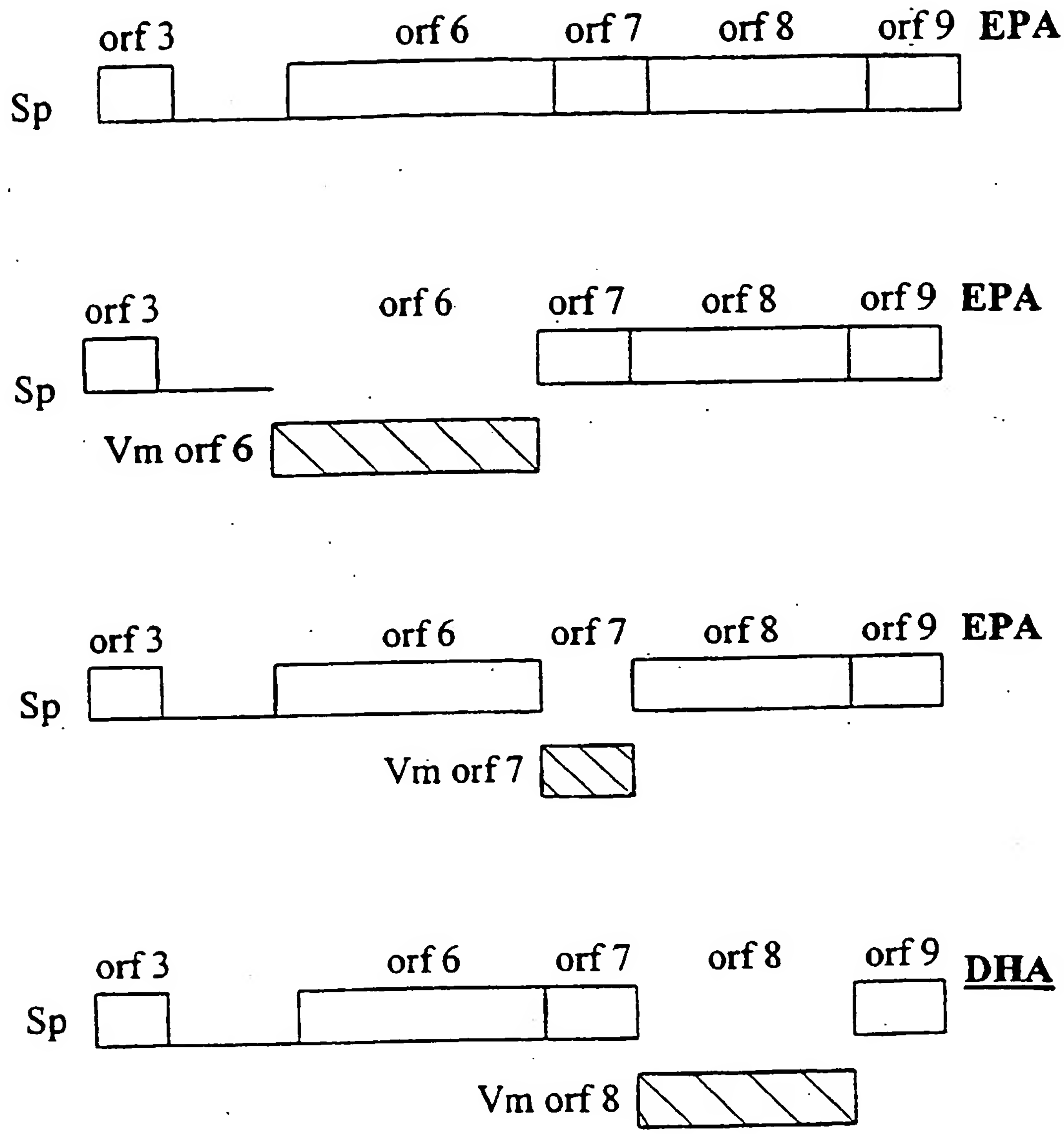


FIG. 12



orf 3
orf 6
orf 7
orf 8
orf 9
EPA
Sp
orf 3
orf 6
orf 7
orf 8
orf 9
EPA
Sp
Vm orf 6
orf 3
orf 6
orf 7
orf 8
orf 9
EPA
Sp
Vm orf 7
orf 3
orf 6
orf 7
orf 8
orf 9
DHA
Sp
Vm orf 8

FIG. 13

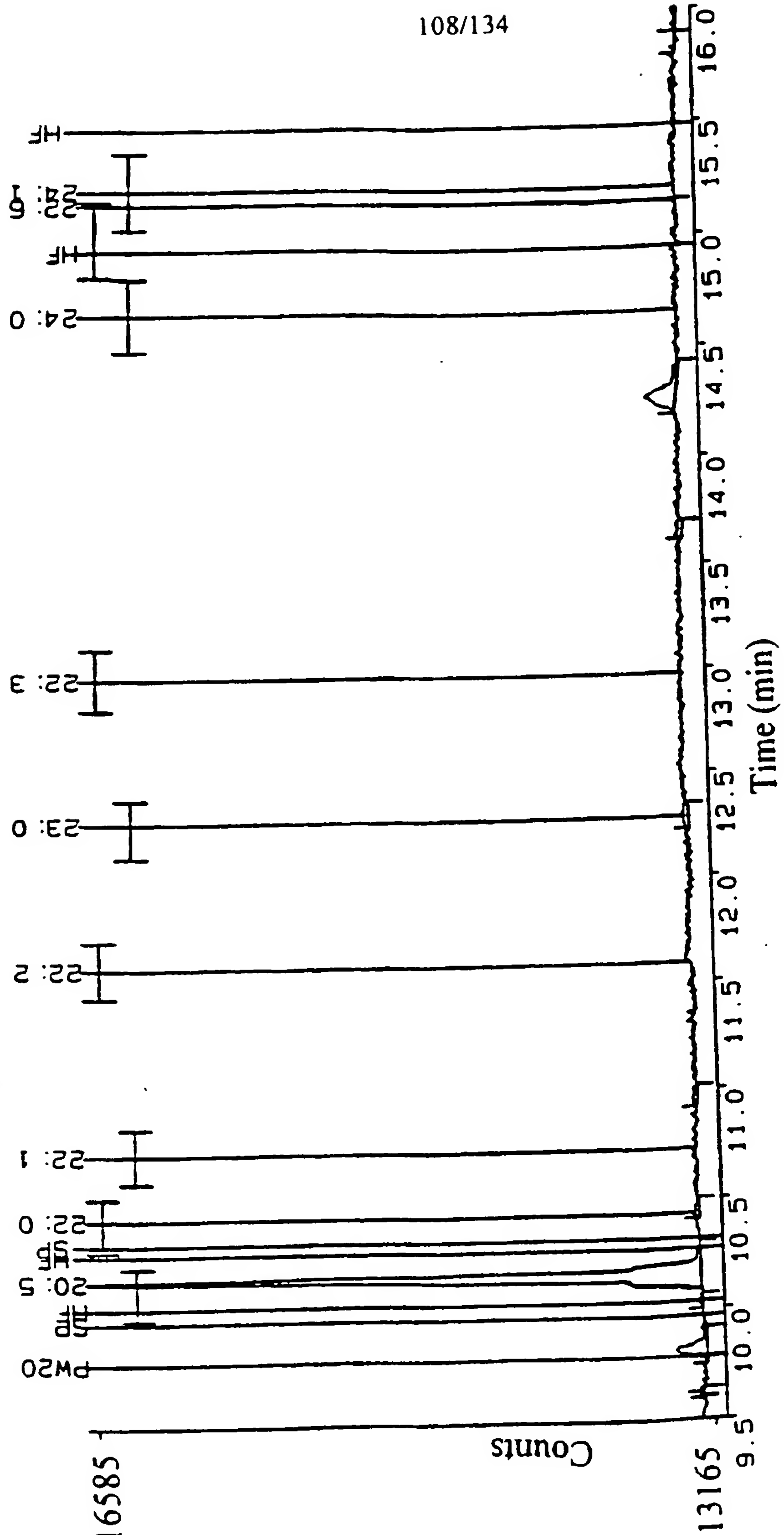

16585
Counts
13165
9.5
10.0
10.5
11.0
11.5
12.0
12.5
13.0
13.5
14.0
14.5
15.0
15.5
16.0
Time (min)

FIG. 14

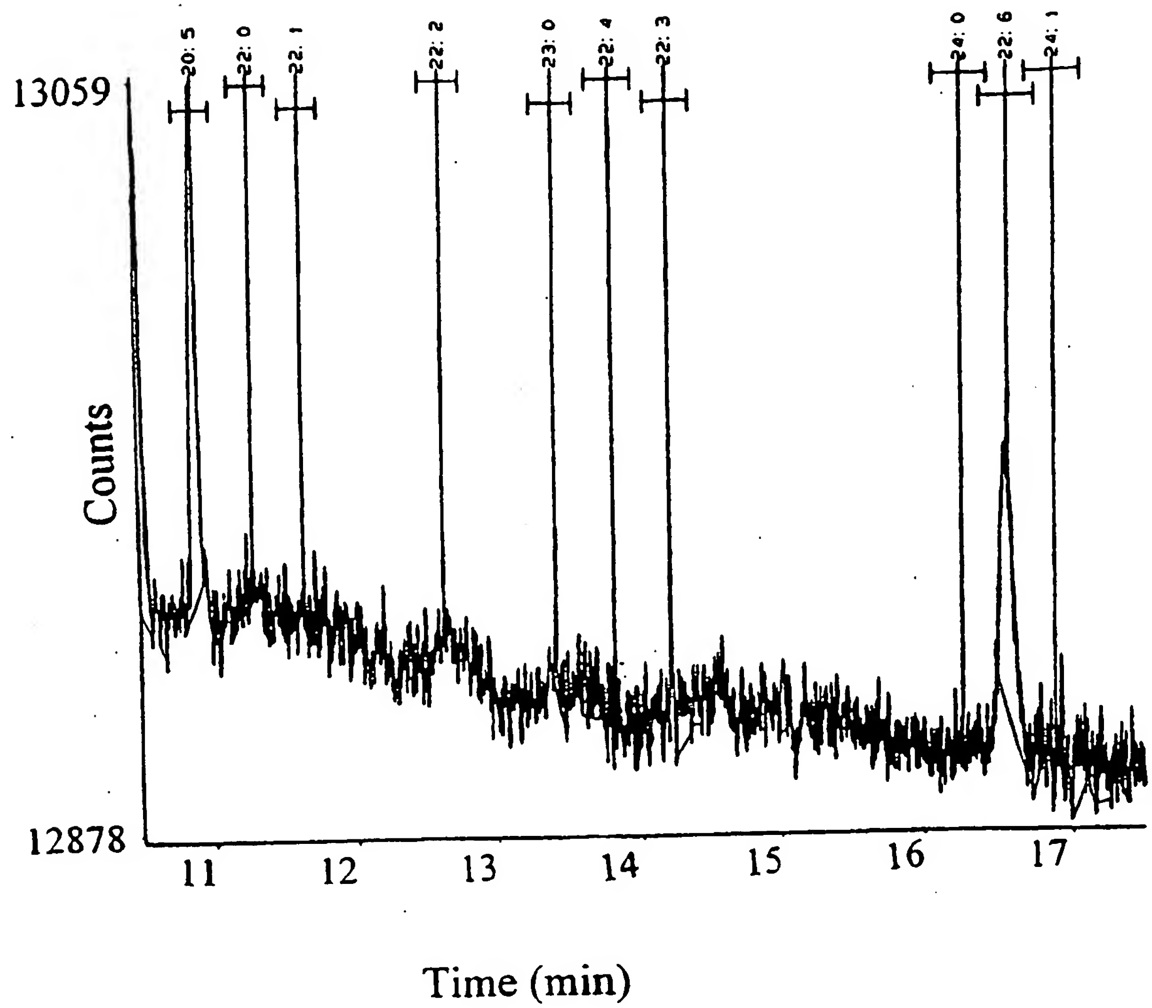

20: 5
22: 0
22: 1
22: 2
23: 0
22: 4
22: 3
24: 0
22: 6
24: 1
13059
12878
Counts
11
12
13
14
15
16
17
Time (min)

FIG. 15

EPA (%Fatty acids)	DHA (%Fatty acids)	20 deg C
0.00	0.06	pEPAD8
0.60	**0.70**	*4*
0.64	**0.66**	*5*
0.33	**0.22**	*6s*
0.45	**0.59**	*6l*
		23 deg C
0.02	0.06	*pEPAD8*
0.32	**0.62**	*4*
0.27	**0.22**	*6s*
0.18	**0.65**	*6l*

FIGURE 16

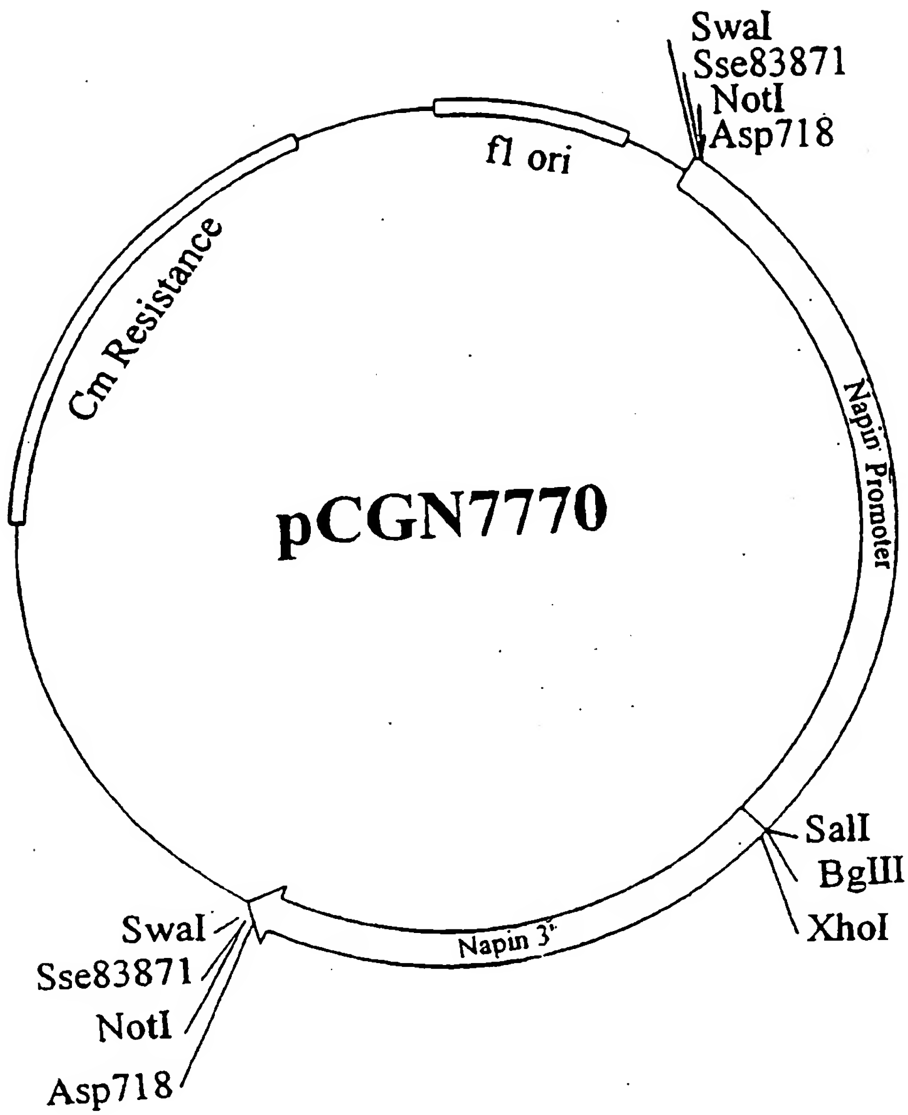

SwaI
Sse83871
NotI
Asp718
f1 ori
Cm Resistance
pCGN7770
Napin Promoter
SalI
BglII
XhoI
Napin 3'
SwaI
Sse83871
NotI
Asp718

FIG. 17

pCGN8535

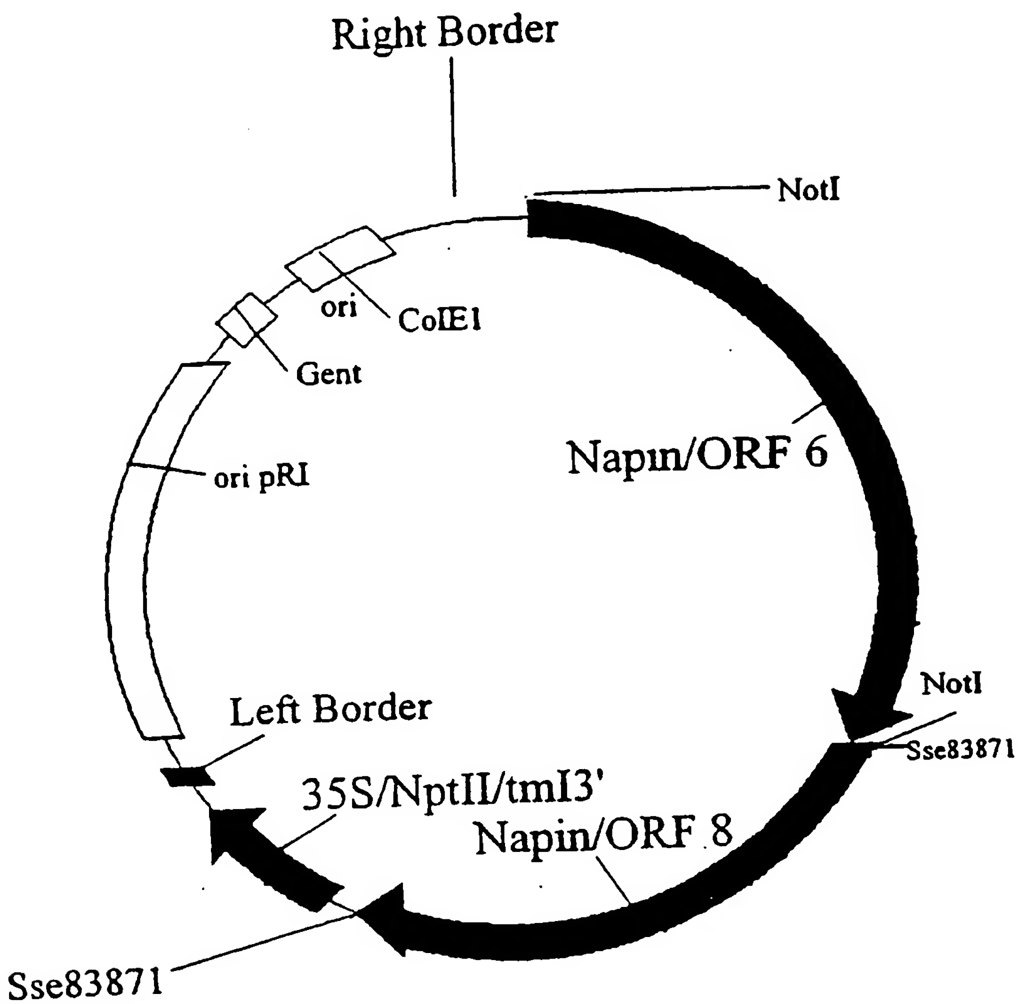


FIG. 18

pCGN8537

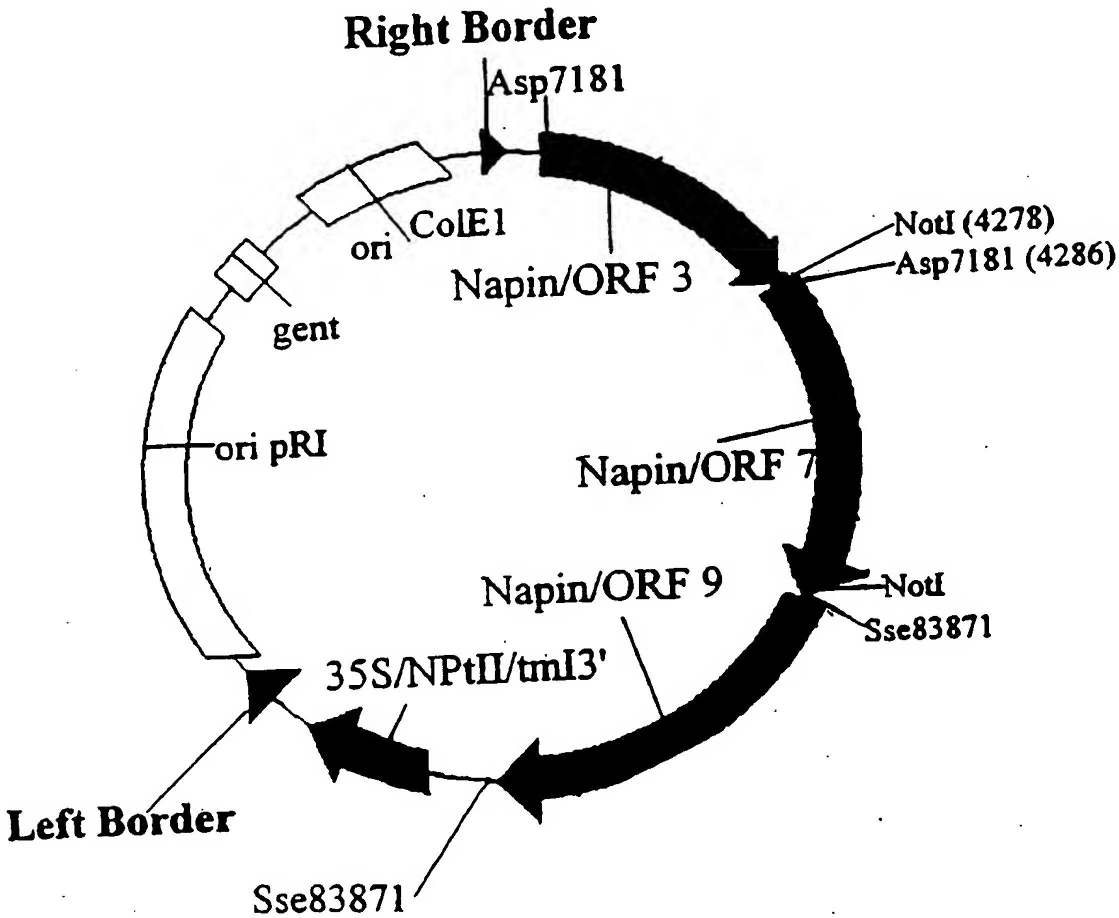


FIG. 19

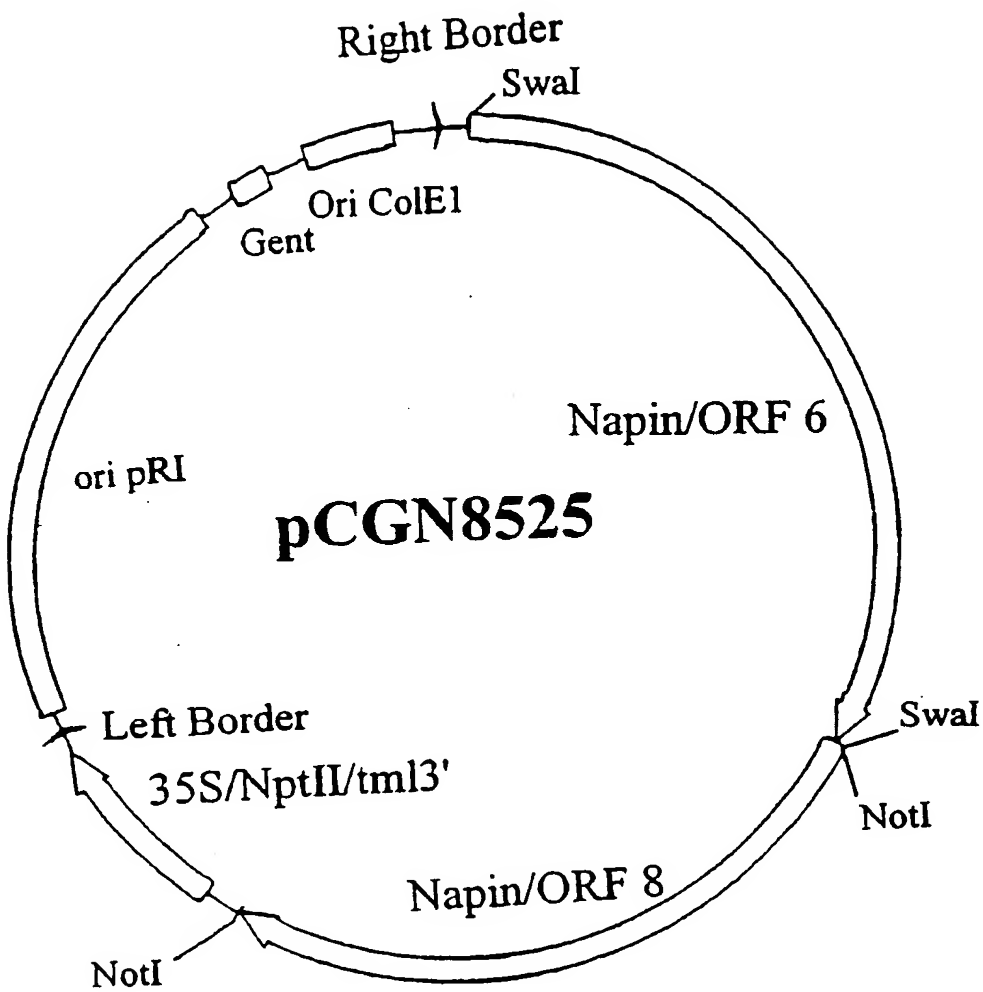

Right Border
SwaI
Ori ColE1
Gent
Napin/ORF 6
ori pRI
pCGN8525
Left Border
35S/NptII/tml3'
SwaI
NotI
Napin/ORF 8
NotI

FIG. 20

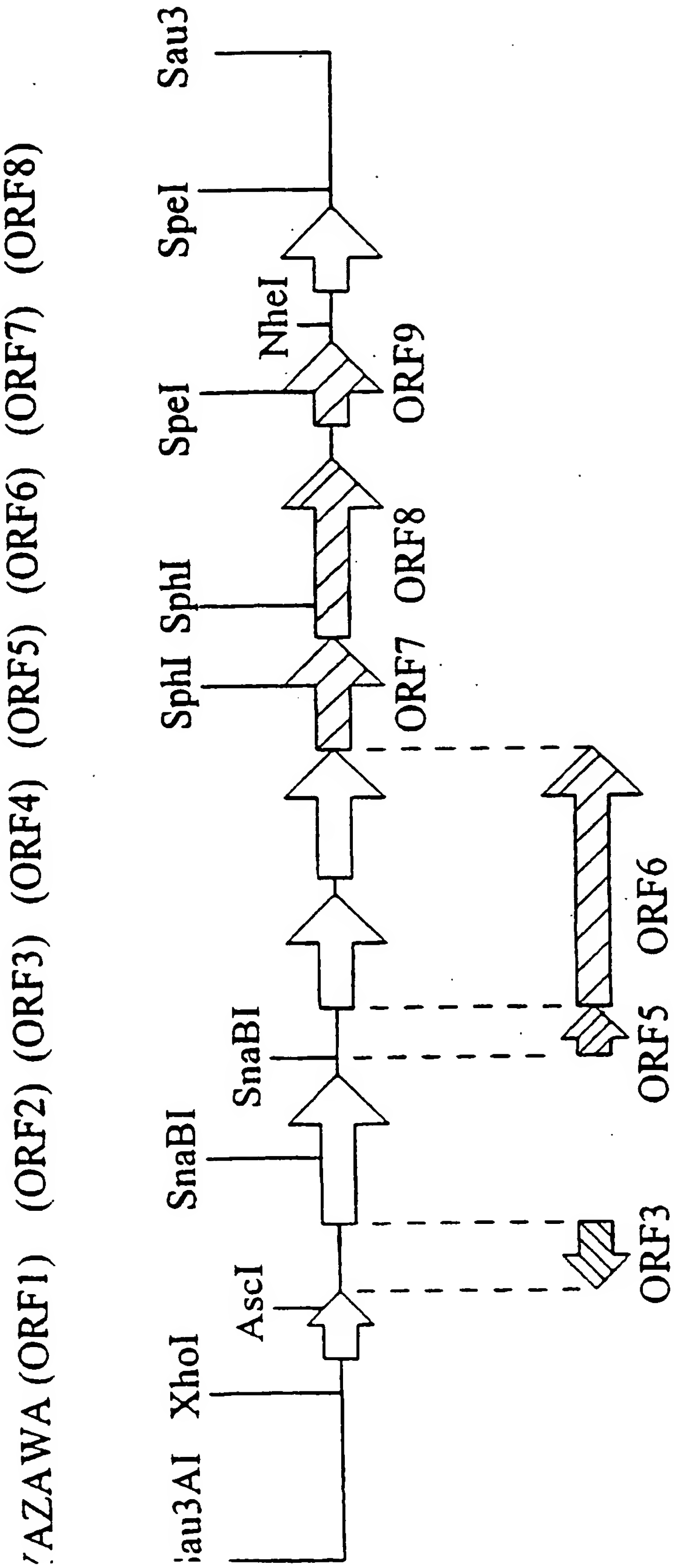

AZAWA (ORF1) (ORF2) (ORF3) (ORF4) (ORF5) (ORF6) (ORF7) (ORF8)
au3AI
XhoI
AscI
SnaBI
SnaBI
SphI
SphI
SpeI
NheI
SpeI
Sau3
ORF3
ORF5
ORF6
ORF7
ORF8
ORF9

FIG. 21

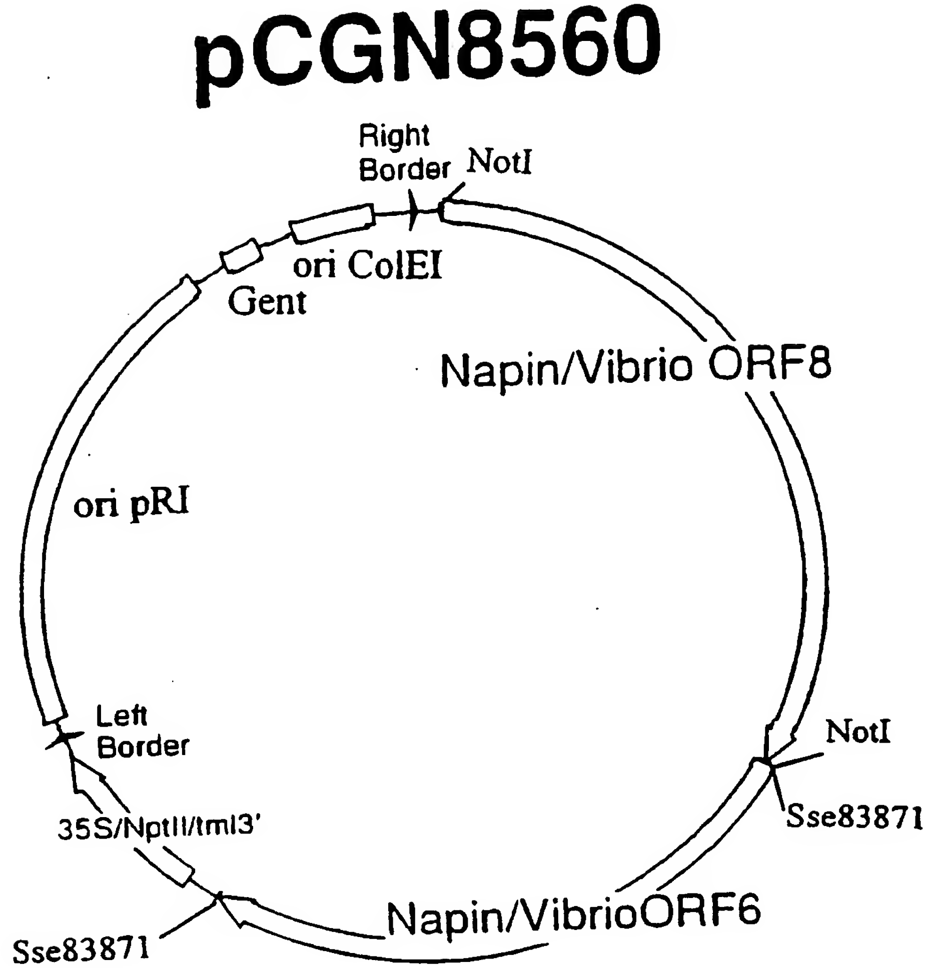

pCGN8560
Right Border
NotI
ori ColEI
Gent
Napin/Vibrio ORF8
ori pRI
NotI
Sse83871
Left Border
35S/NptII/tml3'
Sse83871
Napin/VibrioORF6

FIG. 22

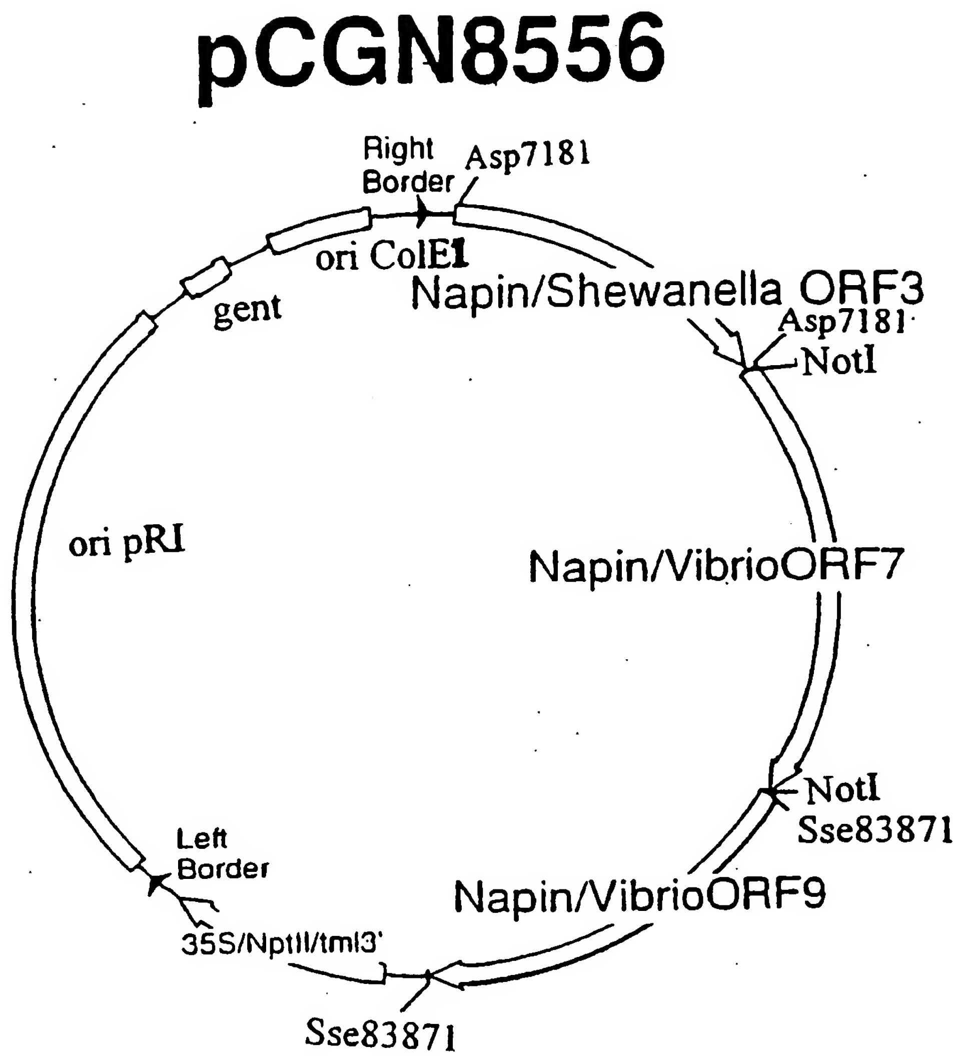

pCGN8556
Right Border
Asp7181
ori ColE1
Napin/Shewanella ORF3
Asp7181
NotI
gent
ori pRI
Napin/VibrioORF7
NotI
Sse83871
Left Border
Napin/VibrioORF9
35S/NptII/tml3'
Sse83871

FIG. 23

ATT GGT AAA AAT AGG GGT TAT GTT TGT TGC TTT AAA GAG TGT CCT GAA
I G K N R G Y V C C F K E C P E

9157

AAA TTG CTA ACT TCT CGA TTG ATT TCC TTA TAC TTC TGT CCG TTA ACA
K L L T S R L I S L Y F C P L T

ATA CAA GAG TGC GAT AAC CAG ACT ACA GAG TTG GTT AAG TCA TGG CTG
I Q E C D N Q T T E L V K S W L

CCT GAA GAT GAG TTA ATT AAG GTT AAT CGC TAC ATT AAA CAA GAA GCT
P E D E L I K V N R Y I K Q E A

9016

AAA ACT CAA GGT TTA ATG GTA AGA G
K T Q G L M V R

FIG. 24

```
AGCGAAATGC TTATCAAGAA ATTCCAAGAT CAATACATCA CTGGGAAGAA AATTCATTCC  60
CTGGTTCACT GGGTAACGTT ATTTCCGGCC GTATTGCTAA CCGCTTCGAC CTTGGTGGCA 120
TGAACTGTGT CGTTGATGCA GCATGTGCAG GCCCTCTTGC TGCATTGCGT ATGGCATTAA 180
GCGAGCTTGT TGAAGGCCGC AGCGAAATGA TGATTACAGG TGGTGTGTGT ACCGATAACT 240
CACCAACCAT GTACATGAGC TTCTCTAAAA CACCGGCATT CACGACAAAC GAAACAATTC 300
AACCATTCGA TATTGACTCG AAAGGTATGA TGATTGGTGA AGGTATCGGT ATGATTGCGC 360
TTAAACGTCT TGAAGACGCA GAGCGTGATG GCGACCGTAT CTATTCCGTG ATTAAAGGTG 420
TTGGGTGCAT CTTCAGACGG TAATTTATTA AGAGTANTTA TGCGCNTCGT CCTGAAGGTC 480
AGGCTAAGGC ACTTAAACGT GCTTACGACG ATGCAGGTTT CGCACCGCAC ACACTTGGCT 540
TACTTGAAGC CCACGGCACA GGCACAGCAG CAGGTGATGT GGCAGAATTC AGTGGTCTTA 600
ACTCTGTATT CAGTGAAGGC AATGACGAAA AGCAACACAT CGCATTAGGT TCAGTGAAAT 660
CACAGATTGG TCACACTAAA TCAACAGCGG GTACTGCGGG TCTAATCAAA GCGTCTTTAG 720
CACTGCACCA TAAAGTACTG CCGCCAACAA TCAATGTAAC CAGCCCTAAC CCTAAACTGA 780
ATATTGAAGA CTCGCCTTTC TACCTCAATA CACAGACGCG TCCATGGATG CAACGTGTCG 840
ATGGTACACC GCGTCGTGCT GGTATTAGCT CATTTGGTTT TGGTG                 885
```

FIG. 25

```
                             20         40         60
                    *         *         *         *         *         *
3-2(-VECTO  CCAAGCTAAA GCACTTAACC GTGCTTATGA AGATGCCGGT TTTGCCCCTG AAACATGTGG

jmpl str +  CCAAGCTAAA GCACTTAACC GTGCCTATGA TGATGCCGGT TTTGCCCCTG AAACATGTGG
            ||||||||||  |||||||||  ||||·|||||  ||||| |||  ||||| ||   ||||||| |
3-2(-VECTO  CCAAGCTAAA GCACTTAACC GTGCTTATGA AGATGCCGGT TTTGCCCCTG AAACATGTGG

                             80        100        120
                    *         *         *         *         *         *
3-2(-VECTO  TCTAATTGAA GGCCATGGTA CGGGTACCAA AGCGGGTGAT GCCGCAGAAT TTGCTGGCTT

jmpl str +
            TCTAATTGAA GGCCATGGTA C
            |||||||||| |  || || | |
3-2(-VECTO  TCTAATTGAA GGCCATGGTA C

jmpl str +
                                    AGA ACGCAAAGTT GCCGCACTGT TTGGTCGCCA
                                    | | ||      | |  ||||||  |  ||||||||
3-2(-VECTO                          CAA AGCGGGTGAT GCCGCACTGT TTGGTCGCTT
```

FIG. 26-1

```
                                 140                 160                 180
                      *          *         *         *         *         *
3-2(-VECTO  GACCAAACAC TTTGGCGCCG CCAGTGATGA AAAGCAATAT ATCGCCTTAG GCTCAGTTAA

jmp1 str +                                            C ATTGCGCTAG GTTCAGTTAA
                                                      | | ||  |||| ||||||||
3-2(-VECTO                                            T ATCGCCTTAG GCTCAGTTAA

jmp1 str +  AGGTTCACAA
                  |||
3-2(-VECTO  GACCTAACAC

                                 200                 220                 240
                      *          *         *         *         *         *
3-2(-VECTO  ATCGCAAATT GGTCATACTA AATCTGCGGC TGGCTCTGCG GGTATGATTA AGGCGGCATT

jmp1 str +                                           CG GCTTCGATTT TGGCGGCATG
                                                     || | |  ||    |    ||||
3-2(-VECTO                                           CG CGTATGATTA AGGCGGCATT

jmp1 str +  ATCACAAATT GGTCATACTA AATCAACTGC AGGT
            ||| |||||| |||||||||| ||||  | ||  ||
3-2(-VECTO  ATCGCAAATT GGTCATACTA AATCTGCGGC TGGC
```

FIG. 26-2

```
jmpl st +                                              GCACTGCT GCAAGCATGA ACGCGTCGTT
                                                       || ||| |  |  ||||  ||||||||
3-2(-VECTO                                             GCTCTGCG GCTATCATTA ACGCGGCATT

                          260                   280                   300
                *         *         *         *         *         *
3-2(-VECTO  AGCGCTGCAT CATAAAATCT TACCTGCAAC GATCCATATC GATAAACCAA GTGAAGCCTT

jmpl st +   AACGGTG
            | |   |
3-2(-VECTO  AGCGCTG

jmpl st +   T
            |
3-2(-VECTO  A

jmpl st +                          TCCCTGGTGC TAACCATATC AGCAAACCA
                                   |   |||    | |||||||   ||| ||
3-2(-VECTO                         TACCTGCAAC GATCCATATC GATAAACCA

                          320                   340                   360
                *         *         *         *         *         *
3-2(-VECTO  GGATATCAAA AACAGCCCGT TATACCTAAA CAGCGAAACG CGTCCTTGGA TGCCACGTGA
```

FIG. 26-3

```
jmpl str +              CTCACCTT TGTATCTAAA CACTGAGACT TCGTCCATGG TTACCACGTGT
                        |   |  | | || ||||| ||  || ||  ||||| |||  | ||||||||
3-2(-VECTO              CAGCCCGT TATACCTAAA CAGCGAAACG GCGTCCTTGG ATGCCACGTGA

                                380                  400
                   *         *          *          *
3-2(-VECTO  AGATGGTATT CCACGTCGTG CAGGTATTAG CTCATTTGGT TTTGGTGGC

jmpl str +  TGATGGTACG CCGCGCCGCG CGGGTATTAG CTCATTTGGT TTTGGTGGC>
             |||||||   || || || | | |||||||| |||||||||| |||||||||
3-2(-VECTO  AGATGGTATT CCACGTCGTG CAGGTATTAG CTCATTTGGT TTTGGTGGC
```

FIG. 26-4

CGCTGCCGCCGCGTCTCGCCGCGCCGCGCCGCGCCGCCGCCGCCGCTCGCGCGCACGCC
CGCGCGTCTCGCCGCGCCTGCTGTCTCGAACGAGCTTCTCGAGAAGGCCGAGACCGTCG
TCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACTGACATGATCGAGTCCGACATG
GAGCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTCGAGATCCTCTCCGAGGT
TCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGACGCTCTCAGCCGCACTCGCACTG
TGGGTGAGGTCGTCAACGCCATGAAGGCTGAGATCGCTGGTGGCTCTGCCCCGGCGCCT
GCCGCCGCTGCCCCAGGTCCGGCTGCTGCCGCCCCTGCGCCTGCTGTCTCGAGCGAGCT
TCTCGAGAAGGCCGAGACTGTCGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGA
CTGACATGATTGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAG
CGTGTCGAGATTCTCTCCGAGGTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGA
CGCTCTCAGCCGCACTCGCACTGTTGGTGAGGTCGTCGATGCCATGAAGGCTGAGATCG
CTGGCAGCTCCGCCTCGGCGCCTGCCGCCGCTGCTCCTGCTCCGGCTGCTGCCGCTCCT
GCGCCCGCTGCCGCCGCCCCTGCTGTCTCGAACGAGCTTCTCGAGAAAGCCGAGACTGT
CGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACTGACATGATCGAGTCCGACA
TGGAGCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTCGAGATCCTCTCCGAG
GTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCCCTCAGCCGCACCCGCAC
TGTTGGCGAGGTTGTCGATGCCATGAAGGCCGAGATCGCTGGTGGCTCTGCCCCGGCGC
CTGCCGCCGCTGCCCCTGCTCCGGCTGCCGCCGCCCCTGCTGTCTCGAACGAGCTTCTT
GAGAAGGCCGAGACTGTCGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACCGA
CATGATCGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAGCGTG
TCGAGATTCTCTCCGAGGTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCT
CTCAGCCGCACTCGCACTGTTGGCGAGGTCGTCGATGCCATGAAGGCTGAGATCGCCGG
CAGCTCCGCCCCGGCGCCTGCCGCCGCTGCTCCTGCTCCGGCTGCTGCCGCTCCTGCGC
CCGCTGCCGCTGCCCCTGCTGTCTCGAGCGAGCTTCTCGAGAAGGCCGAGACCGTCGTC
ATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACTGACATGATTGAGTCCGACATGGA
GCTCGAGACTGAGCTCGGCATTGACTCCATCAAGCGTGTCGAGATCCTCTCCGAGGTTC
AGGCCATGCTCAACGTCGAGGCCAAGGACGTCGATGCCCTCAGCCGCACCCGCACTGTT
GGCGAGGTTGTCGATGCCATGAAGGCCGAGATCGCTGGTGGCTCTGCCCCGGCGCCTGC
CGCCGCTGCCCCTGCTCCGGCTGCCGCCGCCCCTGCTGTCTCGAACGAGCTTCTTGAGA
AGGCCGAGACCGTCGTCATGGAGGTCCTCGCCGCCAAGACTGGCTACGAGACCGACATG
ATCGAGTCCGACATGGAGCTCGAGACCGAGCTCGGCATTGACTCCATCAAGCGTGTCGA
GATTCTCTCCGAGGTTCAGGCCATGCTCAACGTCGAGGCCAAGGACGTCGACGCTCTCA
GCCGCACTCGCACTGTTGGCGAGGTCGTCGATGCCATGAAGGCTGAGATCGCTGGTGGC
TCTGCCCCGGCGCCTGCCGCCGCTGCTCCTGCCTCGGCTGGCGCCGCGCCTGCGGTCAA
GATTGACTCGGTCCACGGCGCTGACTGTGATGATCTTTCCCTGATGCACGCCAAGGTGG
TTGACATCCGCCGCCCGGACGAGCTCATCCTGGAGCGCCCCGAGAACCGCCCCGTTCTC
GTTGTCGATGACGGCAGCGAGCTCACCCTCGCCCTGGTCCGCGTCCTCGGCGCCTGCGC
CGTTGTCCTGACCTTTGAGGGTCTCCAGCTCGCTCAGCGCGCTGGTGCCGCTGCCATCC
GCCACGTGCTCGCCAAGGATCTTTCCGCGGAGAGCGCCGAGAAGGCCATCAAGGAGGCC
GAGCAGCGCTTTGGCGCTCTCGGCGGCTTCATCTCGCAGCAGGCGGAGCGCTTCGAGCC
CGCCGAAATCCTCGGCTTCACGCTCATGTGCGCCAAGTTCGCCAAGGCTTCCCTCTGCA
CGGCTGTGGCTGGCGGCCGCCCGGCCTTTATCGGTGTGGCGCGCCTTGACGGCCGCCTC

Figure 27 A-1

GGATTCACTTCGCAGGGCACTTCTGACGCGCTCAAGCGTGCCCAGCGTGGTGCCATCTT
TGGCCTCTGCAAGACCATCGGCCTCGAGTGGTCCGAGTCTGACGTCTTTTCCCGCGGCG
TGGACATTGCTCAGGGCATGCACCCCGAGGATGCCGCCGTGGCGATTGTGCGCGAGATG
GCGTGCGCTGACATTCGCATTCGCGAGGTCGGCATTGGCGCAAACCAGCAGCGCTGCAC
GATCCGTGCCGCCAAGCTCGAGACCGGCAACCCGCAGCGCCAGATCGCCAAGGACGACG
TGCTGCTCGTTTCTGGCGGCGCTCGCGGCATCACGCCTCTTTGCATCCGGGAGATCACG
CGCCAGATCGCGGGCGGCAAGTACATTCTGCTTGGCCGCAGCAAGGTCTCTGCGAGCGA
ACCGGCATGGTGCGCTGGCATCACTGACGAGAAGGCTGTGCAAAAGGCTGCTACCCAGG
AGCTCAAGCGCGCCTTTAGCGCTGGCGAGGGCCCCAAGCCCACGCCCCGCGCTGTCACT
AAGCTTGTGGGCTCTGTTCTTGGCGCTCGCGAGGTGCGCAGCTCTATTGCTGCGATTGA
AGCGCTCGGCGGCAAGGCCATCTACTCGTCGTGCGACGTGAACTCTGCCGCCGACGTGG
CCAAGGCCGTGCGCGATGCCGAGTCCCAGCTCGGTGCCCGCGTCTCGGGCATCGTTCAT
GCCTCGGGCGTGCTCCGCGACCGTCTCATCGAGAAGAAGCTCCCCGACGAGTTCGACGC
CGTCTTTGGCACCAAGGTCACCGGTCTCGAGAACCTCCTCGCCGCCGTCGACCGCGCCA
ACCTCAAGCACATGGTCCTCTTCAGCTCGCTCGCCGGCTTCCACGGCAACGTCGGCCAG
TCTGACTACGCCATGGCCAACGAGGCCCTTAACAAGATGGGCCTCGAGCTCGCCAAGGA
CGTCTCGGTCAAGTCGATCTGCTTCGGTCCCTGGGACGGTGGCATGGTGACGCCGCAGC
TCAAGAAGCAGTTCCAGGAGATGGGCGTGCAGATCATCCCCCGCGAGGGCGGCGCTGAT
ACCGTGGCGCGCATCGTGCTCGGCTCCTCGCCGGCTGAGATCCTTGTCGGCAACTGGCG
CACCCCGTCCAAGAAGGTCGGCTCGGACACCATCACCCTGCACCGCAAGATTTCCGCCA
AGTCCAACCCCTTCCTCGAGGACCACGTCATCCAGGGCCGCCGCGTGCTGCCCATGACG
CTGGCCATTGGCTCGCTCGCGGAGACCTGCCTCGGCCTCTTCCCCGGCTACTCGCTCTG
GGCCATTGACGACGCCCAGCTCTTCAAGGGTGTCACTGTCGACGGCGACGTCAACTGCG
AGGTGACCCTCACCCCGTCGACGGCGCCCTCGGGCCGCGTCAACGTCCAGGCCACGCTC
AAGACCTTTTCCAGCGGCAAGCTGGTCCCGGCCTACCGCGCCGTCATCGTGCTCTCCAA
CCAGGGCGCGCCCCCGGCCAACGCCACCATGCAGCCGCCCTCGCTCGATGCCGATCCGG
CGCTCCAGGGCTCCGTCTACGACGGCAAGACCCTCTTCCACGGCCCGGCCTTCCGCGGC
ATCGATGACGTGCTCTCGTGCACCAAGAGCCAGCTTGTGGCCAAGTGCAGCGCTGTCCC
CGGCTCCGACGCCGCTCGCGGCGAGTTTGCCACGGACACTGACGCCCATGACCCCTTCG
TGAACGACCTGGCCTTTCAGGCCATGCTCGTCTGGGTGCGCCGCACGCTCGGCCAGGCT
GCGCTCCCCAACTCGATCCAGCGCATCGTCCAGCACCGCCCGGTCCCGCAGGACAAGCC
CTTCTACATTACCCTCCGCTCCAACCAGTCGGGCGGTCACTCCCAGCACAAGCACGCCC
TTCAGTTCCACAACGAGCAGGGCGATCTCTTCATTGATGTCCAGGCTTCGGTCATCGCC
ACGGACAGCCTTGCCTTCTAA

Figure 27 A-2

TGCCGTCTTTGAGGAGCATGACCCCTCCAACGCCGCCTGCACGGCCACGACTCCATTT
CTGCGCTCTCGGCCCGCTGCGGCGGTGAAAGCAACATGCGCATCGCCATCACTGGTATG
GACGCCACCTTTGGCGCTCTCAAGGGACTCGACGCCTTCGAGCGCGCCATTTACACCGG
CGCTCACGGTGCCATCCCACTCCCAGAAAAGCGCTGGCGCTTTCTCGGCAAGGACAAGG
ACTTTCTTGACCTCTGCGGCGTCAAGGCCACCCCGCACGGCTGCTACATTGAAGATGTT
GAGGTCGACTTCCAGCGCCTCCGCACGCCCATGACCCCTGAAGACATGCTCCTCCCTCA
GCAGCTTCTGGCCGTCACCACCATTGACCGCGCCATCCTCGACTCGGGAATGAAAAAGG
GTGGCAATGTCGCCGTCTTTGTCGGCCTCGGCACCGACCTCGAGCTCTACCGTCACCGT
GCTCGCGTCGCTCTCAAGGAGCGCGTCCGCCCTGAAGCCTCCAAGAAGCTCAATGACAT
GATGCAGTACATTAACGACTGCGGCACATCCACATCGTACACCTCGTACATTGGCAACC
TCGTCGCCACGCGCGTCTCGTCGCAGTGGGGCTTCACGGGCCCCTCCTTTACGATCACC
GAGGGCAACAACTCCGTCTACCGCTGCGCCGAGCTCGGCAAGTACCTCCTCGAGACCGG
CGAGGTCGATGGCGTCGTCGTTGCGGGTGTCGATCTCTGCGGCAGTGCCGAAAACCTTT
ACGTCAAGTCTCGCCGCTTCAAGGTGTCCACCTCCGATACCCCGCGCGCCAGCTTTGAC
GCCGCCGCCGATGGCTACTTTGTCGGCGAGGGCTGCGGTGCCTTTGTGCTCAAGCGTGA
GACTAGCTGCACCAAGGACGACCGTATCTACGCTTGCATGGATGCCATCGTCCCTGGCA
ACGTCCCTAGCGCCTGCTTGCGCGAGGCCCTCGACCAGGCGCGCGTCAAGCCGGGCGAT
ATCGAGATGCTCGAGCTCAGCGCCGACTCCGCCCGCCACCTCAAGGACCCGTCCGTCCT
GCCCAAGGAGCTCACTGCCGAGGAGGAAATCGGCGGCCTTCAGACGATCCTTCGTGACG
ATGACAAGCTCCCGCGCAACGTCGCAACGGGCAGTGTCAAGGCCACCGTCGGTGACACC
GGTTATGCCTCTGGTGCTGCCAGCCTCATCAAGGCTGCGCTTTGCATCTACAACCGCTA
CCTGCCCAGCAACGGCGACGACTGGGATGAACCCGCCCCTGAGGCGCCCTGGGACAGCA
CCCTCTTTGCGTGCCAGACCTCGCGCGCTTGGCTCAAGAACCCTGGCGAGCGTCGCTAT
GCGGCCGTCTCGGGCGTCTCCGAGACGCGCTCGTGCTATTCCGTGCTCCTCTCCGAAGC
CGAGGGCCACTACGAGCGCGAGAACCGCATCTCGCTCGACGAGGAGGCGCCCAAGCTCA
TTGTGCTTCGCGCCGACTCCCACGAGGAGATCCTTGGTCGCCTCGACAAGATCCGCGAG
CGCTTCTTGCAGCCCACGGGCGCCGCCCCGCGCGAGTCCGAGCTCAAGGCGCAGGCCCG
CCGCATCTTCCTCGAGCTCCTCGGCGAGACCCTTGCCCAGGATGCCGCTTCTTCAGGCT
CGCAAAAGCCCCTCGCTCTCAGCCTCGTCTCCACGCCCTCCAAGCTCCAGCGCGAGGTC
GAGCTCGCGGCCAAGGGTATCCCGCGCTGCCTCAAGATGCGCCGCGATTGGAGCTCCCC
TGCTGGCAGCCGCTACGCGCCTGAGCCGCTCGCCAGCGACCGCGTCGCCTTCATGTACG
GCGAAGGTCGCAGCCCTTACTACGGCATCACCCAAGACATTCACCGCATTTGGCCCGAA
CTCCACGAGGTCATCAACGAAAAGACGAACCGTCTCTGGGCCGAAGGCGACCGCTGGGT
CATGCCGCGCGCCAGCTTCAAGTCGGAGCTCGAGAGCCAGCAGCAAGAGTTTGATCGCA
ACATGATTGAAATGTTCCGTCTTGGAATCCTCACCTCAATTGCCTTCACCAATCTGGCG
CGCGACGTTCTCAACATCACGCCCAAGGCCGCCTTTGGCCTCAGTCTTGGCGAGATTTC
CATGATTTTTGCCTTTTCCAAGAAGAACGGTCTCATCTCCGACCAGCTCACCAAGGATC
TTCGCGAGTCCGACGTGTGGAACAAGGCTCTGGCCGTTGAATTTAATGCGCTGCGCGAG
GCCTGGGGCATTCCACAGAGTGTCCCCAAGGACGAGTTCTGGCAAGGCTACATTGTGCG
CGGCACCAAGCAGGATATCGAGGCGGCCATCGCCCCGGACAGCAAGTACGTGCGCCTCA
CCATCATCAATGATGCCAACACCGCCCTCATTAGCGGCAAGCCCGACGCCTGCAAGGCT
GCGATCGCGCGTCTCGGTGGCAACATTCCTGCGCTTCCCGTGACCCAGGGCATGTGCGG
CCACTGCCCCGAGGTGGACCTTATACCAAGGATATCGCCAAGATCCATGCCAACCTTG

Figure 27 B-1

AGTTCCCCGTTGTCGACGGCCTTGACCTCTGGACCACAATCAACCAGAAGCGCCTCGTG
CCACGCGCCACGGGCGCCAAGGACGAATGGGCCCCTTCTTCCTTTGGCGAGTACGCCGG
CCAGCTCTACGAGAAGCAGGCTAACTTCCCCCAAATCGTCGAGACCATTTACAAGCAAA
ACTACGACGTCTTTGTCGAGGTTGGGCCCAACAACCACCGTAGCACCGCAGTGCGCACC
ACGCTTGGTCCCCAGCGCAACCACCTTGCTGGCGCCATCGACAAGCAGAACGAGGATGC
TTGGACGACCATCGTCAAGCTTGTGGCTTCGCTCAAGGCCCACCTTGTTCCTGGCGTCA
CGATCTCGCCGCTGTACCACTCCAAGCTTGTGGCGGAGGCTCAGGCTTGCTACGCTGCG
CTCTGCAAGGGTGAAAAGCCCAAGAAGAACAAGTTTGTGCGCAAGATTCAGCTCAACGG
TCGCTTCAACAGCAAGGCGGACCCCATCTCCTCGGCCGATCTTGCCAGCTTTCCGCCTG
CGGACCCTGCCATTGAAGCCGCCATCTCGAGCCGCATCATGAAGCCTGTCGCTCCCAAG
TTCTACGCGCGTCTCAACATTGACGAGCAGGACGAGACCCGAGATCCGATCCTCAACAA
GGACAACGCGCCGTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTTCTC
CGTCGCCTGCTCCTTCGGCCCCCGTGCAAAAGAAGGCTGCTCCCGCCGCGGAGACCAAG
GCTGTTGCTTCGGCTGACGCACTTCGCAGTGCCCTGCTCGATCTCGACAGTATGCTTGC
GCTGAGCTCTGCCAGTGCCTCCGGCAACCTTGTTGAGACTGCGCCTAGCGACGCCTCGG
TCATTGTGCCGCCCTGCAACATTGCGGATCTCGGCAGCCGCGCCTTCATGAAAACGTAC
GGTGTTTCGGCGCCTCTGTACACGGGCGCCATGGCCAAGGGCATTGCCTCTGCGGACCT
CGTCATTGCCGCCGGCCGCCAGGGCATCCTTGCGTCCTTTGGCGCCGGCGGACTTCCCA
TGCAGGTTGTGCGTGAGTCCATCGAAAAGATTCAGGCCGCCCTGCCCAATGGCCCGTAC
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Figure 27 B-2

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Figure 27 B-3

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Figure 27 C-1

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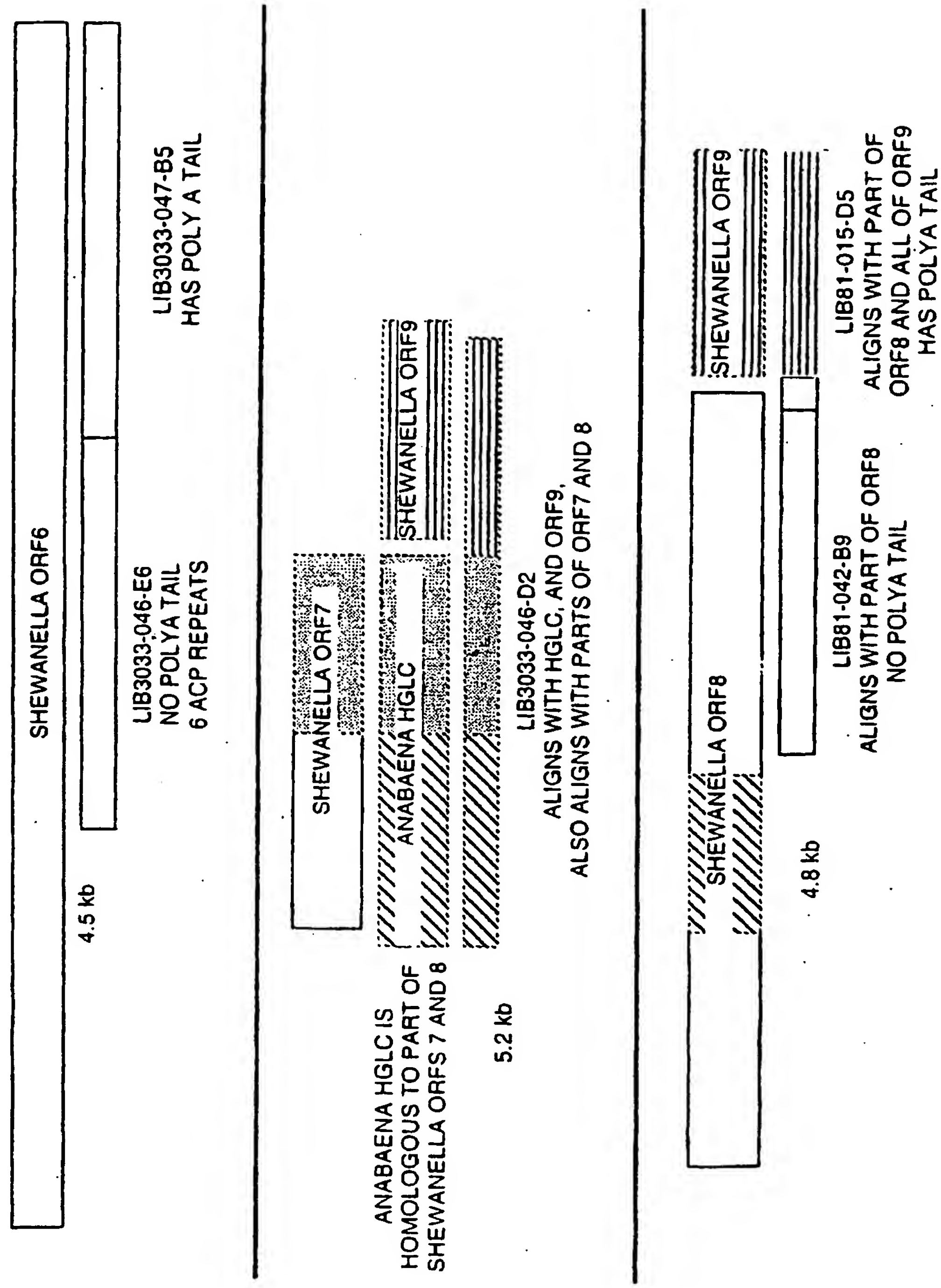
Figure 27 C-2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ANABAENA HGLC
SHEWANELLA ORF9
ANABAENA HGLC IS
HOMOLOGOUS TO PART OF
SHEWANELLA ORFS 7 AND 8
5.2 kb
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ALSO ALIGNS WITH PARTS OF ORF7 AND 8
SHEWANELLA ORF8
SHEWANELLA ORF9
4.8 kb
LIB81-042-B9
ALIGNS WITH PART OF ORF8
NO POLYA TAIL
LIB81-015-D5
ALIGNS WITH PART OF
ORF8 AND ALL OF ORF9
HAS POLYA TAIL

Figure 28

RCRRVSPRRAAPPPPLARTPARLAAPAVSNELLEKAETVVMEVLAAKTGYETDMIESDM
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Figure 29 A

AVFEEHDPSNAACTGHDSISALSARCGGESNMRIAITGMDATFGALKGLDAFERAIYTG
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Figure 29 B

RAEAGREPEPAPQITSTAAESQQQQQQQQQQQQQQQPREGDKEKAAETMALRVKTNKKPCWEMT
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Figure 29 C

SEQUENCE LISTING

<110> Lassner, Michael
Metz, James G
Facciotti, Daniel

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Glu Gly Lys Ala Ala Thr Glu His Thr Ile Ala His Asn Gln Ala Val
35 40 45

Ala Lys Thr Leu Asn Phe Ala Asp Thr Arg Ala Phe Glu Gln Ser Ser
50 55 60

Lys Asn Leu Val Ala Lys Phe Asp Lys Ala Thr Ala Asp Ile Leu Arg
65 70 75 80

Ala Glu Phe Ala Phe Ile Ser Asp Glu Ile Pro Asp Ser Val Asn Pro
85 90 95

Ser Leu Tyr Arg Gln Ala Gln Leu Asn Met Val Pro Asn Gly Tyr Lys
100 105 110

Val Ser Asp Gly Ile Tyr Gln Val Arg Gly Thr Asp Leu Ser Asn Leu
115 120 125

Thr Leu Ile Arg Ser Asp Asn Gly Trp Ile Ala Tyr Asp Val Leu Leu
130 135 140

Thr Lys Glu Ala Ala Lys Ala Ser Leu Gln Phe Ala Leu Lys Asn Leu
145 150 155 160

Pro Lys Asp Gly Asp Pro Val Val Ala Met Ile Tyr Ser His Ser His
165 170 175

Ala Asp His Phe Gly Gly Ala Arg Gly Val Gln Glu Met Phe Pro Asp
180 185 190

Val Lys Val Tyr Gly Ser Asp Asn Ile Thr Lys Glu Ile Val Asp Glu
195 200 205

Asn Val Leu Ala Gly Asn Ala Met Ser Arg Arg Ala Ala Tyr Gln Tyr
210 215 220

Gly Ala Thr Leu Gly Lys His Asp His Gly Ile Val Asp Ala Ala Leu
225 230 235 240

Gly Lys Gly Leu Ser Lys Gly Glu Ile Thr Tyr Val Ala Pro Asp Tyr
245 250 255

Thr Leu Asn Ser Glu Gly Lys Trp Glu Thr Leu Thr Ile Asp Gly Leu
260 265 270

Glu Met Val Phe Met Asp Ala Ser Gly Thr Glu Ala Glu Ser Glu Met

275 280 285

Ile Thr Tyr Ile Pro Ser Lys Lys Ala Leu Trp Thr Ala Glu Leu Thr
290 295 300

Tyr Gln Gly Met His Asn Ile Tyr Thr Leu Arg Gly Ala Lys Val Arg
305 310 315 320

Asp Ala Leu Lys Trp Ser Lys Asp Ile Asn Glu Met Ile Asn Ala Phe
325 330 335

Gly Gln Asp Val Glu Val Leu Phe Ala Ser His Ser Ala Pro Val Trp
340 345 350

Gly Asn Gln Ala Ile Asn Asp Phe Leu Arg Leu Gln Arg Asp Asn Tyr
355 360 365

Gly Leu Val His Asn Gln Thr Leu Arg Leu Ala Asn Asp Gly Val Gly
370 375 380

Ile Gln Asp Ile Gly Asp Ala Ile Gln Asp Thr Ile Pro Glu Ser Ile
385 390 395 400

Tyr Lys Thr Trp His Thr Asn Gly Tyr His Gly Thr Tyr Ser His Asn
405 410 415

Ala Lys Ala Val Tyr Asn Lys Tyr Leu Gly Tyr Phe Asp Met Asn Pro
420 425 430

Ala Asn Leu Asn Pro Leu Pro Thr Lys Gln Glu Ser Ala Lys Phe Val
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Glu Tyr Met Gly Gly Ala Asp Ala Ala Ile Lys Arg Ala Lys Asp Asp
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Tyr Ala Gln Gly Glu Tyr Arg Phe Val Ala Thr Ala Leu Asn Lys Val
465 470 475 480

Val Met Ala Glu Pro Glu Asn Asp Ser Ala Arg Gln Leu Leu Ala Asp
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Thr Tyr Glu Gln Leu Gly Tyr Gln Ala Glu Gly Ala Gly Trp Arg Asn
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Ile Tyr Leu Thr Gly Ala Gln Glu Leu Arg Val Gly Ile Gln Ala Gly
515 520 525

Ala Pro Lys Thr Ala Ser Ala Asp Val Ile Ser Glu Met Asp Met Pro

530 535 540

Thr Leu Phe Asp Phe Leu Ala Val Lys Ile Asp Ser Gln Gln Ala Ala
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Lys His Gly Leu Val Lys Met Asn Val Ile Thr Pro Asp Thr Lys Asp
565 570 575

Ile Leu Tyr Ile Glu Leu Ser Asn Gly Asn Leu Ser Asn Ala Val Val
580 585 590

Asp Lys Glu Gln Leu Met Val Asn Lys Ala Asp Val Asn Arg Ile Leu
595 600 605

Leu Gly Gln Val Thr Leu Lys Ala Leu Leu Ala Ser Gly Asp Ala Lys
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Glu Phe Thr Pro Asp Phe Glu Ile Val Pro Thr Pro Val Lys
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Tyr Ser Asp Asp Leu His Gly Leu Leu Cys His Trp Asn Asp Ala Ala
35 40 45

Asn Met Gln Gln Glu Lys Ala Glu Ile Leu Gly Leu Gly Ser Lys Gln
50 55 60

Pro Glu Ala Asn Pro Lys Asn Ser Ser Ser Glu Leu Leu Ala Leu Gly
65 70 75 80

Ile Asp Gln Lys Leu Leu Val Gln Arg Gln Asn Leu Gln His Glu Val
85 90 95

Lys His Asp Ala Ile Ala Asp Ser Ile Asp Val Cys His Ser Leu Ser
100 105 110

Lys Pro Ala Asn Val Gly Leu Phe Thr Glu Ser Leu Ala Ser Phe Asp
115 120 125

Phe Ala Phe Ser Lys Leu Ser Leu Ala Leu Gly Leu Gly Lys Ala Lys
130 135 140

Ile Tyr Ser Glu Lys Leu Ala Trp Leu Asp Phe Phe Arg Asp Arg Gln
145 150 155 160

Leu Ala Glu Pro Leu Ala Leu Leu Ala Arg Lys Glu Ser Glu Ser Phe
165 170 175

Tyr His Ser Leu Ile Ser His Ile Asn Thr Ser Asn Arg Cys Arg Glu
180 185 190

Ile Asp Val Gly Phe Glu Ile Ser Ala Ser Asp Thr Glu Glu Lys Ser
195 200 205

Ala Gln Ser Ala Gly Lys Asn Asp Ala Thr Cys Ile Gly Val Leu Leu
210 215 220

Trp Asp Gly Ser His Ser Val Asn Phe His Val Gly Thr Gln Ala Phe
225 230 235 240

Gln Ala Asp Ser Leu Arg Pro Lys Gly Lys Asp Gly Tyr Glu Phe Arg
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Trp Glu Asn Pro Arg Ile Glu Ser His Gln Ser Leu Leu Ala Arg Leu
260 265 270

Tyr Gly Arg Val Met
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20 25 30

Glu Thr Ala Ala Glu Glu Gln Ile Glu Arg Val Ala Val Thr Gly Ser
35 40 45

Arg Ile Ala Lys Ala Glu Leu Thr Gln Pro Ala Pro Val Val Ser Leu
50 55 60

Ser Ala Glu Glu Leu Thr Lys Phe Gly Asn Gln Asp Leu Gly Ser Val
65 70 75 80

Leu Ala Glu Leu Pro Ala Ile Gly Ala Thr Asn Thr Ile Ile Gly Asn
85 90 95

Asn Asn Ser Asn Ser Ser Ala Gly Val Ser Ser Ala Asp Leu Arg Arg
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Leu Gly Ala Asn Arg Thr Leu Val Leu Val Asn Gly Lys Arg Tyr Val
115 120 125

Ala Gly Gln Pro Gly Ser Ala Glu Val Asp Leu Ser Thr Ile Pro Thr
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Ser Met Ile Ser Arg Val Glu Ile Val Thr Gly Gly Ala Ser Ala Ile
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Tyr Gly Ser Asp Ala Val Ser Gly Val Ile Asn Val Ile Leu Lys Glu
165 170 175

Asp Phe Glu Gly Phe Glu Phe Asn Ala Arg Thr Ser Gly Ser Thr Glu
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Ser Val Gly Thr Gln Glu His Ser Phe Asp Ile Leu Gly Gly Ala Asn
195 200 205

Val Ala Asp Gly Arg Gly Asn Val Thr Phe Tyr Ala Gly Tyr Glu Arg
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Thr Lys Glu Val Met Ala Thr Asp Ile Arg Gln Phe Asp Ala Trp Gly
225 230 235 240

Thr Ile Lys Asn Glu Ala Asp Gly Gly Glu Asp Asp Gly Ile Pro Asp
245 250 255

Arg Leu Arg Val Pro Arg Val Tyr Ser Glu Met Ile Asn Ala Thr Gly
260 265 270

Val Ile Asn Ala Phe Gly Gly Gly Ile Gly Arg Ser Thr Phe Asp Ser
275 280 285

Asn Gly Asn Pro Ile Ala Gln Gln Glu Arg Asp Gly Thr Asn Ser Phe
290 295 300

Ala Phe Gly Ser Phe Pro Asn Gly Cys Asp Thr Cys Phe Asn Thr Glu
305 310 315 320

Ala Tyr Glu Asn Tyr Ile Pro Gly Val Glu Arg Ile Asn Val Gly Ser
325 330 335

Ser Phe Asn Phe Asp Phe Thr Asp Asn Ile Gln Phe Tyr Thr Asp Phe
340 345 350

Arg Tyr Val Lys Ser Asp Ile Gln Gln Gln Phe Gln Pro Ser Phe Arg
355 360 365

Phe Gly Asn Ile Asn Ile Asn Val Glu Asp Asn Ala Phe Leu Asn Asp
370 375 380

Asp Leu Arg Gln Gln Met Leu Asp Ala Gly Gln Thr Asn Ala Ser Phe
385 390 395 400

Ala Lys Phe Phe Asp Glu Leu Gly Asn Arg Ser Ala Glu Asn Lys Arg
405 410 415

Glu Leu Phe Arg Tyr Val Gly Gly Phe Lys Gly Gly Phe Asp Ile Ser
420 425 430

Glu Thr Ile Phe Asp Tyr Asp Leu Tyr Tyr Val Tyr Gly Glu Thr Asn
435 440 445

Asn Arg Arg Lys Thr Leu Asn Asp Leu Ile Pro Asp Asn Phe Val Ala
450 455 460

Ala Val Asp Ser Val Ile Asp Pro Asp Thr Gly Leu Ala Ala Cys Arg
465 470 475 480

Ser Gln Val Ala Ser Ala Gln Gly Asp Asp Tyr Thr Asp Pro Ala Ser
485 490 495

Val Asn Gly Ser Asp Cys Val Ala Tyr Asn Pro Phe Gly Met Gly Gln
500 505 510

Ala Ser Ala Glu Ala Arg Asp Trp Val Ser Ala Asp Val Thr Arg Glu
515 520 525

Asp Lys Ile Thr Gln Gln Val Ile Gly Gly Thr Leu Gly Thr Asp Ser
530 535 540

Glu Glu Leu Phe Glu Leu Gln Gly Gly Ala Ile Ala Met Val Val Gly
545 550 555 560

Phe Glu Tyr Arg Glu Glu Thr Ser Gly Ser Thr Thr Asp Glu Phe Thr
565 570 575

Lys Ala Gly Phe Leu Thr Ser Ala Ala Thr Pro Asp Ser Tyr Gly Glu
580 585 590

Tyr Asp Val Thr Glu Tyr Phe Val Glu Val Asn Ile Pro Val Leu Lys
595 600 605

Glu Leu Pro Phe Ala His Glu Leu Ser Phe Asp Gly Ala Tyr Arg Asn
610 615 620

Ala Asp Tyr Ser His Ala Gly Lys Thr Glu Ala Trp Lys Ala Gly Met
625 630 635 640

Phe Tyr Ser Pro Leu Glu Gln Leu Ala Leu Arg Gly Thr Val Gly Glu
645 650 655

Ala Val Arg Ala Pro Asn Ile Ala Glu Ala Phe Ser Pro Arg Ser Pro
660 665 670

Gly Phe Gly Arg Val Ser Asp Pro Cys Asp Ala Asp Asn Ile Asn Asp
675 680 685

Asp Pro Asp Arg Val Ser Asn Cys Ala Ala Leu Gly Ile Pro Pro Gly
690 695 700

Phe Gln Ala Asn Asp Asn Val Ser Val Asp Thr Leu Ser Gly Gly Asn
705 710 715 720

Pro Asp Leu Lys Pro Glu Thr Ser Thr Ser Phe Thr Gly Gly Leu Val
725 730 735

Trp Thr Pro Thr Phe Ala Asp Asn Leu Ser Phe Thr Val Asp Tyr Tyr
740 745 750

Asp Ile Gln Ile Glu Asp Ala Ile Leu Ser Val Ala Thr Gln Thr Val
755 760 765

Ala Asp Asn Cys Val Asp Ser Thr Gly Gly Pro Asp Thr Asp Phe Cys
770 775 780

Ser Gln Val Asp Arg Asn Pro Thr Thr Tyr Asp Ile Glu Leu Val Arg
785 790 795 800

Ser Gly Tyr Leu Asn Ala Ala Ala Leu Asn Thr Lys Gly Ile Glu Phe
805 810 815

Gln Ala Ala Tyr Ser Leu Asp Leu Glu Ser Phe Asn Ala Pro Gly Glu
820 825 830

Leu Arg Phe Asn Leu Leu Gly Asn Gln Leu Leu Glu Leu Glu Arg Leu
835 840 845

Glu Phe Gln Asn Arg Pro Asp Glu Ile Asn Asp Glu Lys Gly Glu Val
850 855 860

Gly Asp Pro Glu Leu Gln Phe Arg Leu Gly Ile Asp Tyr Arg Leu Asp
865 870 875 880

Asp Leu Ser Val Ser Trp Asn Thr Arg Tyr Ile Asp Ser Val Val Thr
885 890 895

Tyr Asp Val Ser Glu Asn Gly Gly Ser Pro Glu Asp Leu Tyr Pro Gly
900 905 910

His Ile Gly Ser Met Thr Thr His Asp Leu Ser Ala Thr Tyr Tyr Ile
915 920 925

Asn Glu Asn Phe Met Ile Asn Gly Gly Val Arg Asn Leu Phe Asp Ala
930 935 940

Leu Pro Pro Gly Tyr Thr Asn Asp Ala Leu Tyr Asp Leu Val Gly Arg
945 950 955 960

Arg Ala Phe Leu Gly Ile Lys Val Met Met
965 970

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Thr Thr Pro Glu Met Arg Arg Phe Ile Gln Glu Ser Asp Leu Ser Val
35 40 45

Ser Gln Leu Ser Lys Ile Leu Asn Ile Ser Glu Ala Thr Val Arg Lys
50 55 60

Trp Arg Lys Arg Asp Ser Val Glu Asn Cys Pro Asn Thr Pro His His
65 70 75 80

Leu Asn Thr Thr Leu Thr Pro Leu Gln Glu Tyr Val Val Val Gly Leu
85 90 95

Arg Tyr Gln Leu Lys Met Pro Leu Asp Arg Leu Leu Lys Ala Thr Gln
100 105 110

Glu Phe Ile Asn Pro Asn Val Ser Arg Ser Gly Leu Ala Arg Cys Leu
115 120 125

Lys Arg Tyr Gly Val Ser Arg Val Ser Asp Ile Gln Ser Pro His Val
130 135 140

Pro Met Arg Tyr Phe Asn Gln Ile Pro Val Thr Gln Gly Ser Asp Val
145 150 155 160

Gln Thr Tyr Thr Leu His Tyr Glu Thr Leu Ala Lys Thr Leu Ala Leu
165 170 175

Pro Ser Thr Asp Gly Asp Asn Val Val Gln Val Val Ser Leu Thr Ile
180 185 190

Pro Pro Lys Leu Thr Glu Glu Ala Pro Ser Ser Ile Leu Leu Gly Ile
195 200 205

Asp Pro His Ser Asp Trp Ile Tyr Leu Asp Ile Tyr Gln Asp Gly Asn
210 215 220

Thr Gln Ala Thr Asn Arg Tyr Met Ala Tyr Val Leu Lys His Gly Pro
225 230 235 240

Phe His Leu Arg Lys Leu Leu Val Arg Asn Tyr His Thr Phe Leu Gln
245 250 255

Arg Phe Pro Gly Ala Thr Gln Asn Arg Arg Pro Ser Lys Asp Met Pro
260 265 270

Glu Thr Ile Asn Lys Thr Pro Glu Thr Gln Ala Pro Ser Gly Asp Ser
275 280 285

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Asp Ser Gln Ala Asp Ser Arg Leu Asn Lys Arg Leu Lys Asp Met Pro
20 25 30

Ile Ala Ile Val Gly Met Ala Ser Ile Phe Ala Asn Ser Arg Tyr Leu

35 40 45

Asn Lys Phe Trp Asp Leu Ile Ser Glu Lys Ile Asp Ala Ile Thr Glu
50 55 60

Leu Pro Ser Thr His Trp Gln Pro Glu Glu Tyr Tyr Asp Ala Asp Lys
65 70 75 80

Thr Ala Ala Asp Lys Ser Tyr Cys Lys Arg Gly Gly Phe Leu Pro Asp
85 90 95

Val Asp Phe Asn Pro Met Glu Phe Gly Leu Pro Pro Asn Ile Leu Glu
100 105 110

Leu Thr Asp Ser Ser Gln Leu Leu Ser Leu Ile Val Ala Lys Glu Val
115 120 125

Leu Ala Asp Ala Asn Leu Pro Glu Asn Tyr Asp Arg Asp Lys Ile Gly
130 135 140

Ile Thr Leu Gly Val Gly Gly Gly Gln Lys Ile Ser His Ser Leu Thr
145 150 155 160

Ala Arg Leu Gln Tyr Pro Val Leu Lys Lys Val Phe Ala Asn Ser Gly
165 170 175

Ile Ser Asp Thr Asp Ser Glu Met Leu Ile Lys Lys Phe Gln Asp Gln
180 185 190

Tyr Val His Trp Glu Glu Asn Ser Phe Pro Gly Ser Leu Gly Asn Val
195 200 205

Ile Ala Gly Arg Ile Ala Asn Arg Phe Asp Phe Gly Gly Met Asn Cys
210 215 220

Val Val Asp Ala Ala Cys Ala Gly Ser Leu Ala Ala Met Arg Met Ala
225 230 235 240

Leu Thr Glu Leu Thr Glu Gly Arg Ser Glu Met Met Ile Thr Gly Gly
245 250 255

Val Cys Thr Asp Asn Ser Pro Ser Met Tyr Met Ser Phe Ser Lys Thr
260 265 270

Pro Ala Phe Thr Thr Asn Glu Thr Ile Gln Pro Phe Asp Ile Asp Ser
275 280 285

Lys Gly Met Met Ile Gly Glu Gly Ile Gly Met Val Ala Leu Lys Arg

290 295 300

Leu Glu Asp Ala Glu Arg Asp Gly Asp Arg Ile Tyr Ser Val Ile Lys
305 310 315 320

Gly Val Gly Ala Ser Ser Asp Gly Lys Phe Lys Ser Ile Tyr Ala Pro
325 330 335

Arg Pro Ser Gly Gln Ala Lys Ala Leu Asn Arg Ala Tyr Asp Asp Ala
340 345 350

Gly Phe Ala Pro His Thr Leu Gly Leu Ile Glu Ala His Gly Thr Gly
355 360 365

Thr Ala Ala Gly Asp Ala Ala Glu Phe Ala Gly Leu Cys Ser Val Phe
370 375 380

Ala Glu Gly Asn Asp Thr Lys Gln His Ile Ala Leu Gly Ser Val Lys
385 390 395 400

Ser Gln Ile Gly His Thr Lys Ser Thr Ala Gly Thr Ala Gly Leu Ile
405 410 415

Lys Ala Ala Leu Ala Leu His His Lys Val Leu Pro Pro Thr Ile Asn
420 425 430

Val Ser Gln Pro Ser Pro Lys Leu Asp Ile Glu Asn Ser Pro Phe Tyr
435 440 445

Leu Asn Thr Glu Thr Arg Pro Trp Leu Pro Arg Val Asp Gly Thr Pro
450 455 460

Arg Arg Ala Gly Ile Ser Ser Phe Gly Phe Gly Gly Thr Asn Phe His
465 470 475 480

Phe Val Leu Glu Glu Tyr Asn Gln Glu His Ser Arg Thr Asp Ser Glu
485 490 495

Lys Ala Lys Tyr Arg Gln Arg Gln Val Ala Gln Ser Phe Leu Val Ser
500 505 510

Ala Ser Asp Lys Ala Ser Leu Ile Asn Glu Leu Asn Val Leu Ala Ala
515 520 525

Ser Ala Ser Gln Ala Glu Phe Ile Leu Lys Asp Ala Ala Ala Asn Tyr
530 535 540

Gly Val Arg Glu Leu Asp Lys Asn Ala Pro Arg Ile Gly Leu Val Ala

545 550 555 560

Asn Thr Ala Glu Glu Leu Ala Gly Leu Ile Lys Gln Ala Leu Ala Lys
565 570 575

Leu Ala Ala Ser Asp Asp Asn Ala Trp Gln Leu Pro Gly Gly Thr Ser
580 585 590

Tyr Arg Ala Ala Ala Val Glu Gly Lys Val Ala Ala Leu Phe Ala Gly
595 600 605

Gln Gly Ser Gln Tyr Leu Asn Met Gly Arg Asp Leu Thr Cys Tyr Tyr
610 615 620

Pro Glu Met Arg Gln Gln Phe Val Thr Ala Asp Lys Val Phe Ala Ala
625 630 635 640

Asn Asp Lys Thr Pro Leu Ser Gln Thr Leu Tyr Pro Lys Pro Val Phe
645 650 655

Asn Lys Asp Glu Leu Lys Ala Gln Glu Ala Ile Leu Thr Asn Thr Ala
660 665 670

Asn Ala Gln Ser Ala Ile Gly Ala Ile Ser Met Gly Gln Tyr Asp Leu
675 680 685

Phe Thr Ala Ala Gly Phe Asn Ala Asp Met Val Ala Gly His Ser Phe
690 695 700

Gly Glu Leu Ser Ala Leu Cys Ala Ala Gly Val Ile Ser Ala Asp Asp
705 710 715 720

Tyr Tyr Lys Leu Ala Phe Ala Arg Gly Glu Ala Met Ala Thr Lys Ala
725 730 735

Pro Ala Lys Asp Gly Val Glu Ala Asp Ala Gly Ala Met Phe Ala Ile
740 745 750

Ile Thr Lys Ser Ala Ala Asp Leu Glu Thr Val Glu Ala Thr Ile Ala
755 760 765

Lys Phe Asp Gly Val Lys Val Ala Asn Tyr Asn Ala Pro Thr Gln Ser
770 775 780

Val Ile Ala Gly Pro Thr Ala Thr Thr Ala Asp Ala Ala Lys Ala Leu
785 790 795 800

Thr Glu Leu Gly Tyr Lys Ala Ile Asn Leu Pro Val Ser Gly Ala Phe

805 810 815

His Thr Glu Leu Val Gly His Ala Gln Ala Pro Phe Ala Lys Ala Ile
820 825 830

Asp Ala Ala Lys Phe Thr Lys Thr Ser Arg Ala Leu Tyr Ser Asn Ala
835 840 845

Thr Gly Gly Leu Tyr Glu Ser Thr Ala Ala Lys Ile Lys Ala Ser Phe
850 855 860

Lys Lys His Met Leu Gln Ser Val Arg Phe Thr Ser Gln Leu Glu Ala
865 870 875 880

Met Tyr Asn Asp Gly Ala Arg Val Phe Val Glu Phe Gly Pro Lys Asn
885 890 895

Ile Leu Gln Lys Leu Val Gln Gly Thr Leu Val Asn Thr Glu Asn Glu
900 905 910

Val Cys Thr Ile Ser Ile Asn Pro Asn Pro Lys Val Asp Ser Asp Leu
915 920 925

Gln Leu Lys Gln Ala Ala Met Gln Leu Ala Val Thr Gly Val Val Leu
930 935 940

Ser Glu Ile Asp Pro Tyr Gln Ala Asp Ile Ala Ala Pro Ala Lys Lys
945 950 955 960

Ser Pro Met Ser Ile Ser Leu Asn Ala Ala Asn His Ile Ser Lys Ala
965 970 975

Thr Arg Ala Lys Met Ala Lys Ser Leu Glu Thr Gly Ile Val Thr Ser
980 985 990

Gln Ile Glu His Val Ile Glu Glu Lys Ile Val Glu Val Glu Lys Leu
995 1000 1005

Val Glu Val Glu Lys Ile Val Glu Lys Val Val Glu Val Glu Lys Val
1010 1015 1020

Val Glu Val Glu Ala Pro Val Asn Ser Val Gln Ala Asn Ala Ile Gln
1025 1030 1035 1040

Thr Arg Ser Val Val Ala Pro Val Ile Glu Asn Gln Val Val Ser Lys
1045 1050 1055

Asn Ser Lys Pro Ala Val Gln Ser Ile Ser Gly Asp Ala Leu Ser Asn

1060 1065 1070

Phe Phe Ala Ala Gln Gln Gln Thr Ala Gln Leu His Gln Gln Phe Leu
1075 1080 1085

Ala Ile Pro Gln Gln Tyr Gly Glu Thr Phe Thr Thr Leu Met Thr Glu
1090 1095 1100

Gln Ala Lys Leu Ala Ser Ser Gly Val Ala Ile Pro Glu Ser Leu Gln
1105 1110 1115 1120

Arg Ser Met Glu Gln Phe His Gln Leu Gln Ala Gln Thr Leu Gln Ser
1125 1130 1135

His Thr Gln Phe Leu Glu Met Gln Ala Gly Ser Asn Ile Ala Ala Leu
1140 1145 1150

Asn Leu Leu Asn Ser Ser Gln Ala Thr Tyr Ala Pro Ala Ile His Asn
1155 1160 1165

Glu Ala Ile Gln Ser Gln Val Val Gln Ser Gln Thr Ala Val Gln Pro
1170 1175 1180

Val Ile Ser Thr Gln Val Asn His Val Ser Glu Gln Pro Thr Gln Ala
1185 1190 1195 1200

Pro Ala Pro Lys Ala Gln Pro Ala Pro Val Thr Thr Ala Val Gln Thr
1205 1210 1215

Ala Pro Ala Gln Val Val Arg Gln Ala Ala Pro Val Gln Ala Ala Ile
1220 1225 1230

Glu Pro Ile Asn Thr Ser Val Ala Thr Thr Thr Pro Ser Ala Phe Ser
1235 1240 1245

Ala Glu Thr Ala Leu Ser Ala Thr Lys Val Gln Ala Thr Met Leu Glu
1250 1255 1260

Val Val Ala Glu Lys Thr Gly Tyr Pro Thr Glu Met Leu Glu Leu Glu
1265 1270 1275 1280

Met Asp Met Glu Ala Asp Leu Gly Ile Asp Ser Ile Lys Arg Val Glu
1285 1290 1295

Ile Leu Gly Thr Val Gln Asp Glu Leu Pro Gly Leu Pro Glu Leu Ser
1300 1305 1310

Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly Glu Ile Val Asp Tyr

1315 1320 1325

Met Gly Ser Lys Leu Pro Ala Glu Gly Ser Met Asn Ser Gln Leu Ser
1330 1335 1340

Thr Gly Ser Ala Ala Ala Thr Pro Ala Ala Asn Gly Leu Ser Ala Glu
1345 1350 1355 1360

Lys Val Gln Ala Thr Met Met Ser Val Val Ala Glu Lys Thr Gly Tyr
1365 1370 1375

Pro Thr Glu Met Leu Glu Leu Glu Met Asp Met Glu Ala Asp Leu Gly
1380 1385 1390

Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu
1395 1400 1405

Leu Pro Gly Leu Pro Glu Leu Ser Pro Glu Asp Leu Ala Glu Cys Arg
1410 1415 1420

Thr Leu Gly Glu Ile Val Asp Tyr Met Asn Ser Lys Leu Ala Asp Gly
1425 1430 1435 1440

Ser Lys Leu Pro Ala Glu Gly Ser Met Asn Ser Gln Leu Ser Thr Ser
1445 1450 1455

Ala Ala Ala Ala Thr Pro Ala Ala Asn Gly Leu Ser Ala Glu Lys Val
1460 1465 1470

Gln Ala Thr Met Met Ser Val Val Ala Glu Lys Thr Gly Tyr Pro Thr
1475 1480 1485

Glu Met Leu Glu Leu Glu Met Asp Met Glu Ala Asp Leu Gly Ile Asp
1490 1495 1500

Ser Ile Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu Leu Pro
1505 1510 1515 1520

Gly Leu Pro Glu Leu Asn Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu
1525 1530 1535

Gly Glu Ile Val Thr Tyr Met Asn Ser Lys Leu Ala Asp Gly Ser Lys
1540 1545 1550

Leu Pro Ala Glu Gly Ser Met His Tyr Gln Leu Ser Thr Ser Thr Ala
1555 1560 1565

Ala Ala Thr Pro Val Ala Asn Gly Leu Ser Ala Glu Lys Val Gln Ala

1570 1575 1580

Thr Met Met Ser Val Val Ala Asp Lys Thr Gly Tyr Pro Thr Glu Met
1585 1590 1595 1600

Leu Glu Leu Glu Met Asp Met Glu Ala Asp Leu Gly Ile Asp Ser Ile
1605 1610 1615

Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu Leu Pro Gly Leu
1620 1625 1630

Pro Glu Leu Asn Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly Glu
1635 1640 1645

Ile Val Asp Tyr Met Gly Ser Lys Leu Pro Ala Glu Gly Ser Ala Asn
1650 1655 1660

Thr Ser Ala Ala Ala Ser Leu Asn Val Ser Ala Val Ala Ala Pro Gln
1665 1670 1675 1680

Ala Ala Ala Thr Pro Val Ser Asn Gly Leu Ser Ala Glu Lys Val Gln
1685 1690 1695

Ser Thr Met Met Ser Val Val Ala Glu Lys Thr Gly Tyr Pro Thr Glu
1700 1705 1710

Met Leu Glu Leu Gly Met Asp Met Glu Ala Asp Leu Gly Ile Asp Ser
1715 1720 1725

Ile Lys Arg Val Glu Ile Leu Gly Thr Val Gln Asp Glu Leu Pro Gly
1730 1735 1740

Leu Pro Glu Leu Asn Pro Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly
1745 1750 1755 1760

Glu Ile Val Asp Tyr Met Asn Ser Lys Leu Ala Asp Gly Ser Lys Leu
1765 1770 1775

Pro Ala Glu Gly Ser Ala Asn Thr Ser Ala Thr Ala Ala Thr Pro Ala
1780 1785 1790

Val Asn Gly Leu Ser Ala Asp Lys Val Gln Ala Thr Met Met Ser Val
1795 1800 1805

Val Ala Glu Lys Thr Gly Tyr Pro Thr Glu Met Leu Glu Leu Gly Met
1810 1815 1820

Asp Met Glu Ala Asp Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile

1825 1830 1835 1840

Leu Gly Thr Val Gln Asp Glu Leu Pro Gly Leu Pro Glu Leu Asn Pro
1845 1850 1855

Glu Asp Leu Ala Glu Cys Arg Thr Leu Gly Glu Ile Val Ser Tyr Met
1860 1865 1870

Asn Ser Gln Leu Ala Asp Gly Ser Lys Leu Ser Thr Ser Ala Ala Glu
1875 1880 1885

Gly Ser Ala Asp Thr Ser Ala Ala Asn Ala Ala Lys Pro Ala Ala Ile
1890 1895 1900

Ser Ala Glu Pro Ser Val Glu Leu Pro Pro His Ser Glu Val Ala Leu
1905 1910 1915 1920

Lys Lys Leu Asn Ala Ala Asn Lys Leu Glu Asn Cys Phe Ala Ala Asp
1925 1930 1935

Ala Ser Val Val Ile Asn Asp Asp Gly His Asn Ala Gly Val Leu Ala
1940 1945 1950

Glu Lys Leu Ile Lys Gln Gly Leu Lys Val Ala Val Val Arg Leu Pro
1955 1960 1965

Lys Gly Gln Pro Gln Ser Pro Leu Ser Ser Asp Val Ala Ser Phe Glu
1970 1975 1980

Leu Ala Ser Ser Gln Glu Ser Glu Leu Glu Ala Ser Ile Thr Ala Val
1985 1990 1995 2000

Ile Ala Gln Ile Glu Thr Gln Val Gly Ala Ile Gly Gly Phe Ile His
2005 2010 2015

Leu Gln Pro Glu Ala Asn Thr Glu Glu Gln Thr Ala Val Asn Leu Asp
2020 2025 2030

Ala Gln Ser Phe Thr His Val Ser Asn Ala Phe Leu Trp Ala Lys Leu
2035 2040 2045

Leu Gln Pro Lys Leu Val Ala Gly Ala Asp Ala Arg Arg Cys Phe Val
2050 2055 2060

Thr Val Ser Arg Ile Asp Gly Gly Phe Gly Tyr Leu Asn Thr Asp Ala
2065 2070 2075 2080

Leu Lys Asp Ala Glu Leu Asn Gln Ala Ala Leu Ala Gly Leu Thr Lys

2085 2090 2095

Thr Leu Ser His Glu Trp Pro Gln Val Phe Cys Arg Ala Leu Asp Ile
2100 2105 2110

Ala Thr Asp Val Asp Ala Thr His Leu Ala Asp Ala Ile Thr Ser Glu
2115 2120 2125

Leu Phe Asp Ser Gln Ala Gln Leu Pro Glu Val Gly Leu Ser Leu Ile
2130 2135 2140

Asp Gly Lys Val Asn Arg Val Thr Leu Val Ala Ala Glu Ala Ala Asp
2145 2150 2155 2160

Lys Thr Ala Lys Ala Glu Leu Asn Ser Thr Asp Lys Ile Leu Val Thr
2165 2170 2175

Gly Gly Ala Lys Gly Val Thr Phe Glu Cys Ala Leu Ala Leu Ala Ser
2180 2185 2190

Arg Ser Gln Ser His Phe Ile Leu Ala Gly Arg Ser Glu Leu Gln Ala
2195 2200 2205

Leu Pro Ser Trp Ala Glu Gly Lys Gln Thr Ser Glu Leu Lys Ser Ala
2210 2215 2220

Ala Ile Ala His Ile Ile Ser Thr Gly Gln Lys Pro Thr Pro Lys Gln
2225 2230 2235 2240

Val Glu Ala Ala Val Trp Pro Val Gln Ser Ser Ile Glu Ile Asn Ala
2245 2250 2255

Ala Leu Ala Ala Phe Asn Lys Val Gly Ala Ser Ala Glu Tyr Val Ser
2260 2265 2270

Met Asp Val Thr Asp Ser Ala Ala Ile Thr Ala Ala Leu Asn Gly Arg
2275 2280 2285

Ser Asn Glu Ile Thr Gly Leu Ile His Gly Ala Gly Val Leu Ala Asp
2290 2295 2300

Lys His Ile Gln Asp Lys Thr Leu Ala Glu Leu Ala Lys Val Tyr Gly
2305 2310 2315 2320

Thr Lys Val Asn Gly Leu Lys Ala Leu Leu Ala Ala Leu Glu Pro Ser
2325 2330 2335

Lys Ile Lys Leu Leu Ala Met Phe Ser Ser Ala Ala Gly Phe Tyr Gly

2340 2345 2350

Asn Ile Gly Gln Ser Asp Tyr Ala Met Ser Asn Asp Ile Leu Asn Lys
2355 2360 2365

Ala Ala Leu Gln Phe Thr Ala Arg Asn Pro Gln Ala Lys Val Met Ser
2370 2375 2380

Phe Asn Trp Gly Pro Trp Asp Gly Gly Met Val Asn Pro Ala Leu Lys
2385 2390 2395 2400

Lys Met Phe Thr Glu Arg Gly Val Tyr Val Ile Pro Leu Lys Ala Gly
2405 2410 2415

Ala Glu Leu Phe Ala Thr Gln Leu Leu Ala Glu Thr Gly Val Gln Leu
2420 2425 2430

Leu Ile Gly Thr Ser Met Gln Gly Gly Ser Asp Thr Lys Ala Thr Glu
2435 2440 2445

Thr Ala Ser Val Lys Lys Leu Asn Ala Gly Glu Val Leu Ser Ala Ser
2450 2455 2460

His Pro Arg Ala Gly Ala Gln Lys Thr Pro Leu Gln Ala Val Thr Ala
2465 2470 2475 2480

Thr Arg Leu Leu Thr Pro Ser Ala Met Val Phe Ile Glu Asp His Arg
2485 2490 2495

Ile Gly Gly Asn Ser Val Leu Pro Thr Val Cys Ala Ile Asp Trp Met
2500 2505 2510

Arg Glu Ala Ala Ser Asp Met Leu Gly Ala Gln Val Lys Val Leu Asp
2515 2520 2525

Tyr Lys Leu Leu Lys Gly Ile Val Phe Glu Thr Asp Glu Pro Gln Glu
2530 2535 2540

Leu Thr Leu Glu Leu Thr Pro Asp Asp Ser Asp Glu Ala Thr Leu Gln
2545 2550 2555 2560

Ala Leu Ile Ser Cys Asn Gly Arg Pro Gln Tyr Lys Ala Thr Leu Ile
2565 2570 2575

Ser Asp Asn Ala Asp Ile Lys Gln Leu Asn Lys Gln Phe Asp Leu Ser
2580 2585 2590

Ala Lys Ala Ile Thr Thr Ala Lys Glu Leu Tyr Ser Asn Gly Thr Leu

2595 2600 2605

Phe His Gly Pro Arg Leu Gln Gly Ile Gln Ser Val Val Gln Phe Asp
2610 2615 2620

Asp Gln Gly Leu Ile Ala Lys Val Ala Leu Pro Lys Val Glu Leu Ser
2625 2630 2635 2640

Asp Cys Gly Glu Phe Leu Pro Gln Thr His Met Gly Gly Ser Gln Pro
2645 2650 2655

Phe Ala Glu Asp Leu Leu Leu Gln Ala Met Leu Val Trp Ala Arg Leu
2660 2665 2670

Lys Thr Gly Ser Ala Ser Leu Pro Ser Ser Ile Gly Glu Phe Thr Ser
2675 2680 2685

Tyr Gln Pro Met Ala Phe Gly Glu Thr Gly Thr Ile Glu Leu Glu Val
2690 2695 2700

Ile Lys His Asn Lys Arg Ser Leu Glu Ala Asn Val Ala Leu Tyr Arg
2705 2710 2715 2720

Asp Asn Gly Glu Leu Ser Ala Met Phe Lys Ser Ala Lys Ile Thr Ile
2725 2730 2735

Ser Lys Ser Leu Asn Ser Ala Phe Leu Pro Ala Val Leu Ala Asn Asp
2740 2745 2750

Ser Glu Ala Asn
2755

<210> 8
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Met Pro Leu Arg Ile Ala Leu Ile Leu Leu Pro Thr Pro Gln Phe Glu
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Val Asn Ser Val Asp Gln Ser Val Leu Ala Ser Tyr Gln Thr Leu Gln
20 25 30

Pro Glu Leu Asn Ala Leu Leu Asn Ser Ala Pro Thr Pro Glu Met Leu
35 40 45

Ser Ile Thr Ile Ser Asp Asp Ser Asp Ala Asn Ser Phe Glu Ser Gln
50 55 60

Leu Asn Ala Ala Thr Asn Ala Ile Asn Asn Gly Tyr Ile Val Lys Leu
65 70 75 80

Ala Thr Ala Thr His Ala Leu Leu Met Leu Pro Ala Leu Lys Ala Ala
85 90 95

Gln Met Arg Ile His Pro His Ala Gln Leu Ala Ala Met Gln Gln Ala
100 105 110

Lys Ser Thr Pro Met Ser Gln Val Ser Gly Glu Leu Lys Leu Gly Ala
115 120 125

Asn Ala Leu Ser Leu Ala Gln Thr Asn Ala Leu Ser His Ala Leu Ser
130 135 140

Gln Ala Lys Arg Asn Leu Thr Asp Val Ser Val Asn Glu Cys Phe Glu
145 150 155 160

Asn Leu Lys Ser Glu Gln Gln Phe Thr Glu Val Tyr Ser Leu Ile Gln
165 170 175

Gln Leu Ala Ser Arg Thr His Val Arg Lys Glu Val Asn Gln Gly Val
180 185 190

Glu Leu Gly Pro Lys Gln Ala Lys Ser His Tyr Trp Phe Ser Glu Phe
195 200 205

His Gln Asn Arg Val Ala Ala Ile Asn Phe Ile Asn Gly Gln Gln Ala
210 215 220

Thr Ser Tyr Val Leu Thr Gln Gly Ser Gly Leu Leu Ala Ala Lys Ser
225 230 235 240

Met Leu Asn Gln Gln Arg Leu Met Phe Ile Leu Pro Gly Asn Ser Gln
245 250 255

Gln Gln Ile Thr Ala Ser Ile Thr Gln Leu Met Gln Gln Leu Glu Arg
260 265 270

Leu Gln Val Thr Glu Val Asn Glu Leu Ser Leu Glu Cys Gln Leu Glu
275 280 285

Leu Leu Ser Ile Met Tyr Asp Asn Leu Val Asn Ala Asp Lys Leu Thr
290 295 300

Thr Arg Asp Ser Lys Pro Ala Tyr Gln Ala Val Ile Gln Ala Ser Ser
305 310 315 320

Val Ser Ala Ala Lys Gln Glu Leu Ser Ala Leu Asn Asp Ala Leu Thr
325 330 335

Ala Leu Phe Ala Glu Gln Thr Asn Ala Thr Ser Thr Asn Lys Gly Leu
340 345 350

Ile Gln Tyr Lys Thr Pro Ala Gly Ser Tyr Leu Thr Leu Thr Pro Leu
355 360 365

Gly Ser Asn Asn Asp Asn Ala Gln Ala Gly Leu Ala Phe Val Tyr Pro
370 375 380

Gly Val Gly Thr Val Tyr Ala Asp Met Leu Asn Glu Leu His Gln Tyr
385 390 395 400

Phe Pro Ala Leu Tyr Ala Lys Leu Glu Arg Glu Gly Asp Leu Lys Ala
405 410 415

Met Leu Gln Ala Glu Asp Ile Tyr His Leu Asp Pro Lys His Ala Ala
420 425 430

Gln Met Ser Leu Gly Asp Leu Ala Ile Ala Gly Val Gly Ser Ser Tyr
435 440 445

Leu Leu Thr Gln Leu Leu Thr Asp Glu Phe Asn Ile Lys Pro Asn Phe
450 455 460

Ala Leu Gly Tyr Ser Met Gly Glu Ala Ser Met Trp Ala Ser Leu Gly
465 470 475 480

Val Trp Gln Asn Pro His Ala Leu Ile Ser Lys Thr Gln Thr Asp Pro
485 490 495

Leu Phe Thr Ser Ala Ile Ser Gly Lys Leu Thr Ala Val Arg Gln Ala
500 505 510

Trp Gln Leu Asp Asp Thr Ala Ala Glu Ile Gln Trp Asn Ser Phe Val
515 520 525

Val Arg Ser Glu Ala Ala Pro Ile Glu Ala Leu Leu Lys Asp Tyr Pro
530 535 540

His Ala Tyr Leu Ala Ile Ile Gln Gly Asp Thr Cys Val Ile Ala Gly
545 550 555 560

Cys Glu Ile Gln Cys Lys Ala Leu Leu Ala Ala Leu Gly Lys Arg Gly
565 570 575

Ile Ala Ala Asn Arg Val Thr Ala Met His Thr Gln Pro Ala Met Gln
580 585 590

Glu His Gln Asn Val Met Asp Phe Tyr Leu Gln Pro Leu Lys Ala Glu
595 600 605

Leu Pro Ser Glu Ile Ser Phe Ile Ser Ala Ala Asp Leu Thr Ala Lys
610 615 620

Gln Thr Val Ser Glu Gln Ala Leu Ser Ser Gln Val Val Ala Gln Ser
625 630 635 640

Ile Ala Asp Thr Phe Cys Gln Thr Leu Asp Phe Thr Ala Leu Val His
645 650 655

His Ala Gln His Gln Gly Ala Lys Leu Phe Val Glu Ile Gly Ala Asp
660 665 670

Arg Gln Asn Cys Thr Leu Ile Asp Lys Ile Val Lys Gln Asp Gly Ala
675 680 685

Ser Ser Val Gln His Gln Pro Cys Cys Thr Val Pro Met Asn Ala Lys
690 695 700

Gly Ser Gln Asp Ile Thr Ser Val Ile Lys Ala Leu Gly Gln Leu Ile
705 710 715 720

Ser His Gln Val Pro Leu Ser Val Gln Pro Phe Ile Asp Gly Leu Lys
725 730 735

Arg Glu Leu Thr Leu Cys Gln Leu Thr Ser Gln Gln Leu Ala Ala His
740 745 750

Ala Asn Val Asp Ser Lys Phe Glu Ser Asn Gln Asp His Leu Leu Gln
755 760 765

Gly Glu Val
770

<210> 9
<211> 2004
<212> PRT
<213> Shewanella putrefaciens

<400> 9

Met Ser Leu Pro Asp Asn Ala Ser Asn His Leu Ser Ala Asn Gln Lys
1 5 10 15

Gly Ala Ser Gln Ala Ser Lys Thr Ser Lys Gln Ser Lys Ile Ala Ile
20 25 30

Val Gly Leu Ala Thr Leu Tyr Pro Asp Ala Lys Thr Pro Gln Glu Phe
35 40 45

Trp Gln Asn Leu Leu Asp Lys Arg Asp Ser Arg Ser Thr Leu Thr Asn
50 55 60

Glu Lys Leu Gly Ala Asn Ser Gln Asp Tyr Gln Gly Val Gln Gly Gln
65 70 75 80

Ser Asp Arg Phe Tyr Cys Asn Lys Gly Gly Tyr Ile Glu Asn Phe Ser
85 90 95

Phe Asn Ala Ala Gly Tyr Lys Leu Pro Glu Gln Ser Leu Asn Gly Leu
100 105 110

Asp Asp Ser Phe Leu Trp Ala Leu Asp Thr Ser Arg Asn Ala Leu Ile
115 120 125

Asp Ala Gly Ile Asp Ile Asn Gly Ala Asp Leu Ser Arg Ala Gly Val
130 135 140

Val Met Gly Ala Leu Ser Phe Pro Thr Thr Arg Ser Asn Asp Leu Phe
145 150 155 160

Leu Pro Ile Tyr His Ser Ala Val Glu Lys Ala Leu Gln Asp Lys Leu
165 170 175

Gly Val Lys Ala Phe Lys Leu Ser Pro Thr Asn Ala His Thr Ala Arg
180 185 190

Ala Ala Asn Glu Ser Ser Leu Asn Ala Ala Asn Gly Ala Ile Ala His
195 200 205

Asn Ser Ser Lys Val Val Ala Asp Ala Leu Gly Leu Gly Gly Ala Gln
210 215 220

Leu Ser Leu Asp Ala Ala Cys Ala Ser Ser Val Tyr Ser Leu Lys Leu
225 230 235 240

Ala Cys Asp Tyr Leu Ser Thr Gly Lys Ala Asp Ile Met Leu Ala Gly
245 250 255

Ala Val Ser Gly Ala Asp Pro Phe Phe Ile Asn Met Gly Phe Ser Ile
260 265 270

Phe His Ala Tyr Pro Asp His Gly Ile Ser Val Pro Phe Asp Ala Ser
275 280 285

Ser Lys Gly Leu Phe Ala Gly Glu Gly Ala Gly Val Leu Val Leu Lys
290 295 300

Arg Leu Glu Asp Ala Glu Arg Asp Asn Asp Lys Ile Tyr Ala Val Val
305 310 315 320

Ser Gly Val Gly Leu Ser Asn Asp Gly Lys Gly Gln Phe Val Leu Ser
325 330 335

Pro Asn Pro Lys Gly Gln Val Lys Ala Phe Glu Arg Ala Tyr Ala Ala
340 345 350

Ser Asp Ile Glu Pro Lys Asp Ile Glu Val Ile Glu Cys His Ala Thr
355 360 365

Gly Thr Pro Leu Gly Asp Lys Ile Glu Leu Thr Ser Met Glu Thr Phe
370 375 380

Phe Glu Asp Lys Leu Gln Gly Thr Asp Ala Pro Leu Ile Gly Ser Ala
385 390 395 400

Lys Ser Asn Leu Gly His Leu Leu Thr Ala Ala His Ala Gly Ile Met
405 410 415

Lys Met Ile Phe Ala Met Lys Glu Gly Tyr Leu Pro Pro Ser Ile Asn
420 425 430

Ile Ser Asp Ala Ile Ala Ser Pro Lys Lys Leu Phe Gly Lys Pro Thr
435 440 445

Leu Pro Ser Met Val Gln Gly Trp Pro Asp Lys Pro Ser Asn Asn His
450 455 460

Phe Gly Val Arg Thr Arg His Ala Gly Val Ser Val Phe Gly Phe Gly
465 470 475 480

Gly Cys Asn Ala His Leu Leu Leu Glu Ser Tyr Asn Gly Lys Gly Thr
485 490 495

Val Lys Ala Glu Ala Thr Gln Val Pro Arg Gln Ala Glu Pro Leu Lys
500 505 510

Val Val Gly Leu Ala Ser His Phe Gly Pro Leu Ser Ser Ile Asn Ala
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Leu Asn Asn Ala Val Thr Gln Asp Gly Asn Gly Phe Ile Glu Leu Pro
530 535 540

Lys Lys Arg Trp Lys Gly Leu Glu Lys His Ser Glu Leu Leu Ala Glu
545 550 555 560

Phe Gly Leu Ala Ser Ala Pro Lys Gly Ala Tyr Val Asp Asn Phe Glu
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Leu Asp Phe Leu Arg Phe Lys Leu Pro Pro Asn Glu Asp Asp Arg Leu
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Ile Ser Gln Gln Leu Met Leu Met Arg Val Thr Asp Glu Ala Ile Arg
595 600 605

Asp Ala Lys Leu Glu Pro Gly Gln Lys Val Ala Val Leu Val Ala Met
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Glu Thr Glu Leu Glu Leu His Gln Phe Arg Gly Arg Val Asn Leu His
625 630 635 640

Thr Gln Leu Ala Gln Ser Leu Ala Ala Met Gly Val Ser Leu Ser Thr
645 650 655

Asp Glu Tyr Gln Ala Leu Glu Ala Ile Ala Met Asp Ser Val Leu Asp
660 665 670

Ala Ala Lys Leu Asn Gln Tyr Thr Ser Phe Ile Gly Asn Ile Met Ala
675 680 685

Ser Arg Val Ala Ser Leu Trp Asp Phe Asn Gly Pro Ala Phe Thr Ile
690 695 700

Ser Ala Ala Glu Gln Ser Val Ser Arg Cys Ile Asp Val Ala Gln Asn
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Leu Ile Met Glu Asp Asn Leu Asp Ala Val Val Ile Ala Ala Val Asp
725 730 735

Leu Ser Gly Ser Phe Glu Gln Val Ile Leu Lys Asn Ala Ile Ala Pro
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Val Ala Ile Glu Pro Asn Leu Glu Ala Ser Leu Asn Pro Thr Ser Ala
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Ser Trp Asn Val Gly Glu Gly Ala Gly Ala Val Val Leu Val Lys Asn
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Glu Ala Thr Ser Gly Cys Ser Tyr Gly Gln Ile Asp Ala Leu Gly Phe
785 790 795 800

Ala Lys Thr Ala Glu Thr Ala Leu Ala Thr Asp Lys Leu Leu Ser Gln
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820 825 830

Pro Ala Ser Gln Ile Gln Leu Ala Pro Ile Val Ser Ser Gln Val Thr
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His Thr Ala Ala Glu Gln Arg Val Gly His Cys Phe Ala Ala Ala Gly
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Met Ala Ser Leu Leu His Gly Leu Leu Asn Leu Asn Thr Val Ala Gln
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Thr Asn Lys Ala Asn Cys Ala Leu Ile Asn Asn Ile Ser Glu Asn Gln
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Thr Ala Arg Leu Ser Asn Glu Leu Lys Ser Asp Ala Lys His Gln Leu
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Val Lys Gln Val Thr Leu Gly Gly Arg Asp Ile Tyr Gln His Ile Val
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Asp Thr Pro Leu Ala Ser Leu Glu Ser Ile Thr Gln Lys Leu Ala Gln
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Gly Ser Val Glu Met Ala Asn Ser Phe Glu Thr Glu Ser Ser Ala Glu
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Pro Gln Ile Thr Ile Ala Ala Gln Gln Thr Ala Asn Ile Gly Val Thr
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Ala Gly Asn Thr Val Ala Ser Lys Val Gly Ser Gly Asp Ile Val Asn
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Thr Gln Ala Val Asp Thr Gln Thr Ser Glu Asn Val Ala Ile Ala Ala
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Glu Ser Pro Val Gln Val Thr Thr Pro Val Gln Val Thr Thr Pro Val
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Gln Ile Ser Val Val Glu Leu Lys Pro Asp His Ala Asn Val Pro Pro
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Tyr Thr Pro Pro Val Pro Ala Leu Lys Pro Cys Ile Trp Asn Tyr Ala
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Asp Tyr Ala Ile Ile Asp Ser Tyr Ser Arg Arg Val Arg Leu Pro Thr
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Thr Asp Tyr Leu Leu Val Ser Arg Val Thr Lys Leu Asp Ala Thr Ile
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Asp Ala Pro Tyr Leu Val Asp Gly Gln Ile Pro Trp Ala Val Ala Val
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Gly Gly Cys Ala Gly Phe Phe Thr Asp Glu Glu Leu Ala Asp Gly Lys
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Lys Gln Arg Phe Asn Pro Leu Leu Asp Cys Pro Lys Thr Gln Phe Ser
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Tyr Gly Asp Ile His Lys Leu Leu Thr Ala Asp Ile Glu Gly Cys Phe
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Asp His Trp Tyr Phe Pro Cys His Phe Lys Gly Asp Gln Val Met Ala
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Gly Ser Leu Met Ala Glu Gly Cys Gly Gln Leu Leu Gln Phe Tyr Met
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Thr Ala Gln Val Asn Ala Gln Thr Ser Ala Lys Lys Val Tyr Lys Pro
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Ala Ser Val Asn Ala Pro Leu Met Ala Gln Ile Pro Asp Leu Thr Lys
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Glu Pro Asn Lys Gly Val Ile Pro Ile Ser His Val Glu Ala Pro Ile
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Thr Pro Asp Tyr Pro Asn Arg Val Pro Asp Thr Val Pro Phe Thr Pro
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Tyr His Met Phe Glu Phe Ala Thr Gly Asn Ile Glu Asn Cys Phe Gly
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Pro Glu Phe Ser Ile Tyr Arg Gly Met Ile Pro Pro Arg Thr Pro Cys
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Gly Asp Leu Gln Val Thr Thr Arg Val Ile Glu Val Asn Gly Lys Arg
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Gly Asp Phe Lys Lys Pro Ser Ser Cys Ile Ala Glu Tyr Glu Val Pro
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Ala Asp Ala Trp Tyr Phe Asp Lys Asn Ser His Gly Ala Val Met Pro
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Tyr Ser Ile Leu Met Glu Ile Ser Leu Gln Pro Asn Gly Phe Ile Ser
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Gly Tyr Met Gly Thr Thr Leu Gly Phe Pro Gly Leu Glu Leu Phe Phe
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Arg Asn Leu Asp Gly Ser Gly Glu Leu Leu Arg Glu Val Asp Leu Arg
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Gly Lys Thr Ile Arg Asn Asp Ser Arg Leu Leu Ser Thr Val Met Ala
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Glu Pro Phe Tyr Arg Gly Thr Ala Val Phe Gly Tyr Phe Lys Gly Asp
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Ala Leu Lys Asp Gln Leu Gly Leu Asp Asn Gly Lys Val Thr Gln Pro
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Trp His Val Ala Asn Gly Val Ala Ala Ser Thr Lys Val Asn Leu Leu
1825 1830 1835 1840

Asp Lys Ser Cys Arg His Phe Asn Ala Pro Ala Asn Gln Pro His Tyr
1845 1850 1855

Arg Leu Ala Gly Gly Gln Leu Asn Phe Ile Asp Ser Val Glu Ile Val
1860 1865 1870

Asp Asn Gly Gly Thr Glu Gly Leu Gly Tyr Leu Tyr Ala Glu Arg Thr
1875 1880 1885

Ile Asp Pro Ser Asp Trp Phe Phe Gln Phe His Phe His Gln Asp Pro
1890 1895 1900

Val Met Pro Gly Ser Leu Gly Val Glu Ala Ile Ile Glu Thr Met Gln
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Ala Tyr Ala Ile Ser Lys Asp Leu Gly Ala Asp Phe Lys Asn Pro Lys
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Phe Gly Gln Ile Leu Ser Asn Ile Lys Trp Lys Tyr Arg Gly Gln Ile
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Asn Pro Leu Asn Lys Gln Met Ser Met Asp Val Ser Ile Thr Ser Ile
1955 1960 1965

Lys Asp Glu Asp Gly Lys Lys Val Ile Thr Gly Asn Ala Ser Leu Ser
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Gly Phe Gly Ile Ala Gln Thr Ala Asp Ile Val Thr Glu Gln Ala Ala
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Asn Ser Thr Asp Leu Pro Val Ser Ala Phe Thr Pro Ala Leu Gly Thr
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Glu Ser Leu Gly Asp Asn Asn Phe Arg Arg Val His Gly Val Lys Tyr
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Ala Tyr Tyr Ala Gly Ala Met Ala Asn Gly Ile Ser Ser Glu Glu Leu
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Val Ile Ala Leu Gly Gln Ala Gly Ile Leu Cys Gly Ser Phe Gly Ala
115 120 125

Ala Gly Leu Ile Pro Ser Arg Val Glu Ala Ala Ile Asn Arg Ile Gln
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Ala Ala Leu Pro Asn Gly Pro Tyr Met Phe Asn Leu Ile His Ser Pro
145 150 155 160

Ser Glu Pro Ala Leu Glu Arg Gly Ser Val Glu Leu Phe Leu Lys His
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Lys Val Arg Thr Val Glu Ala Ser Ala Phe Leu Gly Leu Thr Pro Gln
180 185 190

Ile Val Tyr Tyr Arg Ala Ala Gly Leu Ser Arg Asp Ala Gln Gly Lys
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Val Val Val Gly Asn Lys Val Ile Ala Lys Val Ser Arg Thr Glu Val
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Ala Glu Lys Phe Met Met Pro Ala Pro Ala Lys Met Leu Gln Lys Leu
225 230 235 240

Val Asp Asp Gly Ser Ile Thr Ala Glu Gln Met Glu Leu Ala Gln Leu

245 250 255

Val Pro Met Ala Asp Asp Ile Thr Ala Glu Ala Asp Ser Gly Gly His
260 265 270

Thr Asp Asn Arg Pro Leu Val Thr Leu Leu Pro Thr Ile Leu Ala Leu
275 280 285

Lys Glu Glu Ile Gln Ala Lys Tyr Gln Tyr Asp Thr Pro Ile Arg Val
290 295 300

Gly Cys Gly Gly Gly Val Gly Thr Pro Asp Ala Ala Leu Ala Thr Phe
305 310 315 320

Asn Met Gly Ala Ala Tyr Ile Val Thr Gly Ser Ile Asn Gln Ala Cys
325 330 335

Val Glu Ala Gly Ala Ser Asp His Thr Arg Lys Leu Leu Ala Thr Thr
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Glu Met Ala Asp Val Thr Met Ala Pro Ala Ala Asp Met Phe Glu Met
355 360 365

Gly Val Lys Leu Gln Val Val Lys Arg Gly Thr Leu Phe Pro Met Arg
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Ala Asn Lys Leu Tyr Glu Ile Tyr Thr Arg Tyr Asp Ser Ile Glu Ala
385 390 395 400

Ile Pro Leu Asp Glu Arg Glu Lys Leu Glu Lys Gln Val Phe Arg Ser
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Ser Leu Asp Glu Ile Trp Ala Gly Thr Val Ala His Phe Asn Glu Arg
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Asp Pro Lys Gln Ile Glu Arg Ala Glu Gly Asn Pro Lys Arg Lys Met
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Ala Leu Ile Phe Arg Trp Tyr Leu Gly Leu Ser Ser Arg Trp Ser Asn
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Ser Gly Glu Val Gly Arg Glu Met Asp Tyr Gln Ile Trp Ala Gly Pro
465 470 475 480

Ala Leu Gly Ala Phe Asn Gln Trp Ala Lys Gly Ser Tyr Leu Asp Asn
485 490 495

Tyr Gln Asp Arg Asn Ala Val Asp Leu Ala Lys His Leu Met Tyr Gly

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35 40 45

Asp Gly Val Phe Ile Phe Asn Arg Thr Asn Gln Pro Val Phe Ser Lys
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Gly Phe Asn His Arg Asn Asp Ile Pro Leu Val Phe Glu Leu Thr Asp
65 70 75 80

Phe Lys Gln His Pro Gln Asn Ile Ala Leu Ser Pro Gln Thr Lys Gln
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Ala His Pro Pro Ala Ser Lys Pro Leu Asp Ser Pro Asp Asp Val Pro
100 105 110

Ser Thr His Gly Val Ile Ala Thr Arg Tyr Gly Pro Ala Ile Tyr Tyr
115 120 125

Ser Ser Thr Ser Ile Leu Lys Ser Asp Arg Ser Gly Ser Gln Leu Gly
130 135 140

Tyr Leu Val Phe Ile Arg Leu Ile Asp Glu Trp Phe Ile Ala Glu Leu
145 150 155 160

Ser Gln Tyr Thr Ala Ala Gly Val Glu Ile Ala Met Ala Asp Ala Ala
165 170 175

Asp Ala Gln Leu Ala Arg Leu Gly Ala Asn Thr Lys Leu Asn Lys Val
180 185 190

Thr Ala Thr Ser Glu Arg Leu Ile Thr Asn Val Asp Gly Lys Pro Leu
195 200 205

Leu Lys Leu Val Leu Tyr His Thr Asn Asn Gln Pro Pro Pro Met Leu
210 215 220

Asp Tyr Ser Ile Ile Ile Leu Leu Val Glu Met Ser Phe Leu Leu Ile
225 230 235 240

Leu Ala Tyr Phe Leu Tyr Ser Tyr Phe Leu Val Arg Pro Val Arg Lys
245 250 255

Leu Ala Ser Asp Ile Lys Lys Met Asp Lys Ser Arg Glu Ile Lys Lys
260 265 270

Leu Arg Tyr His Tyr Pro Ile Thr Glu Leu Val Lys Val Ala Thr His
275 280 285

Phe Asn Ala Leu Met Gly Thr Ile Gln Glu Gln Thr Lys Gln Leu Asn
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Glu Gln Val Phe Ile Asp Lys Leu Thr Asn Ile Pro Asn Arg Arg Ala
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Phe Glu Gln Arg Leu Glu Thr Tyr Cys Gln Leu Leu Ala Arg Gln Gln
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Ile Gly Phe Thr Leu Ile Ile Ala Asp Val Asp His Phe Lys Glu Tyr
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Asn Asp Thr Leu Gly His Leu Ala Gly Asp Glu Ala Leu Ile Lys Val
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Ala Gln Thr Leu Ser Gln Gln Phe Tyr Arg Ala Glu Asp Ile Cys Ala
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Arg Phe Gly Gly Glu Glu Phe Ile Met Leu Phe Arg Asp Ile Pro Asp
385 390 395 400

Glu Pro Leu Gln Arg Lys Leu Asp Ala Met Leu His Ser Phe Ala Glu
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Leu Asn Leu Pro His Pro Asn Ser Ser Thr Ala Asn Tyr Val Thr Val
420 425 430

Ser Leu Gly Val Cys Thr Val Val Ala Val Asp Asp Phe Glu Phe Lys
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Ser Glu Ser His Ile Ile Gly Ser Gln Ala Ala Leu Ile Ala Asp Lys
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Ala Leu Tyr His Ala Lys Ala Cys Gly Arg Asn Gln Ala Leu Ser Lys
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gtgttgtaac tcgaaattgc ccctttc 19227

<210> 14
<211> 217
<212> DNA
<213> Shewanella putrefaciens

<400> 14
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tctcgattga tttccttata cttctgtccg ttaacaatac aagagtgcga taaccagact 120
acagagttgg ttaagtcatg gctgcctgaa gatgagttaa ttaaggttaa tcgctacatt 180
aaacaagaag ctaaaactca aggtttaatg gtaagag 217

<210> 15
<211> 72
<212> PRT
<213> Shewanella putrefaciens

<400> 15
Ile Gly Lys Asn Arg Gly Tyr Val Cys Cys Phe Lys Glu Cys Pro Glu
1 5 10 15

Lys Leu Leu Thr Ser Arg Leu Ile Ser Leu Tyr Phe Cys Pro Leu Thr
20 25 30

Ile Gln Glu Cys Asp Asn Gln Thr Thr Glu Leu Val Lys Ser Trp Leu
35 40 45

Pro Glu Asp Glu Leu Ile Lys Val Asn Arg Tyr Ile Lys Gln Glu Ala
50 55 60

Lys Thr Gln Gly Leu Met Val Arg
65 70

<210> 16
<211> 885
<212> DNA

<213> Shewanella putrefaciens

<400> 16
agcgaaatgc ttatcaagaa attccaagat caatacatca ctgggaagaa aattcattcc 60
ctggttcact gggtaacgtt atttccggcc gtattgctaa ccgcttcgac cttggtggca 120
tgaactgtgt cgttgatgca gcatgtgcag gccctcttgc tgcattgcgt atggcattaa 180
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cactgcacca taaagtactg ccgccaacaa tcaatgtaac cagccctaac cctaaactga 780
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<210> 17
<211> 409
<212> DNA
<213> Shewanella putrefaciens

<400> 17
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ggatatcaaa aacagcccgt tatacctaaa cagcgaaacg cgtccttgga tgccacgtga 360
agatggtatt ccacgtcgtg caggtattag ctcatttggt tttggtggc 409

<210> 18
<211> 81
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 18
ccaagctaaa gcacttaacc gtgcctatga tgatgccggt tttgcccctg aaacatgtgg 60
tctaattgaa ggccatggta c 81

<210> 19
<211> 81
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 19
ccaagctaaa gcacttaacc gtgcttatga agatgccggt tttgcccctg aaacatgtgg 60
tctaattgaa ggccatggta c 81

<210> 20
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 20
agaacgcaaa gttgccgcac tgtttggtcg ccaaggttca caa 43

<210> 21
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 21
caaagcgggt gatgccgcac tgtttggtcg cttgacctaa cac 43

<210> 22
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 22
cattgcgcta ggttcagtta aatcacaaat tggtcatact aaatcaactg caggt 55

<210> 23
<211> 55
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: SYNTHETIC

<400> 23
tatcgcctta ggctcagtta aatcgcaaat tggtcatact aaatctgcgg ctggc 55

<210> 24
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 24
cggcttcgat tttggcggca tgaacggtg 29

<210> 25
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 25
cgcgtatgat taaggcggca ttagcgctg 29

<210> 26
<211> 28
<212> DNA
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<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 26
gcactgctgc aagcatgaac gcgtcgtt 28

<210> 27
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 27
gctctgcggc tatcattaac gcggcatt 28

<210> 28
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 28
tccctggtgc taaccatatc agcaaacca 29

<210> 29
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 29
tacctgcaac gatccatatc gataaacca 29

<210> 30
<211> 98
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 30
ctcacctttg tatctaaaca ctgagacttc gtccatggtt accacgtgtt gatggtacgc 60
cgcgccgcgc gggtattagc tcatttggtt ttggtggc 98

<210> 31
<211> 98
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: SYNTHETIC

<400> 31
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cacgtcgtgc aggtattagc tcatttggtt ttggtggc 98

<210> 32

<211> 4
<212> PRT
<213> Shewanella putrefaciens

<400> 32
Asp Xaa Ala Cys
1

<210> 33
<211> 4
<212> PRT
<213> Shewanella putrefaciens

<400> 33
Gly Phe Gly Gly
1

<210> 34
<211> 5
<212> PRT
<213> Shewanella putrefaciens

<400> 34
Gly His Ser Xaa Gly
1 5

<210> 35
<211> 6
<212> PRT
<213> Shewanella putrefaciens

<400> 35
Leu Gly Xaa Asp Ser Leu
1 5

<210> 36
<211> 6
<212> PRT
<213> Shewanella putrefaciens

<400> 36
Leu Gly Xaa Asp Ser Ile
1 5

<210> 37
<211> 6
<212> PRT
<213> Shewanella putrefaciens

<400> 37
Gly Xaa Gly Xaa Xaa Gly
1 5

<210> 38
<211> 6
<212> PRT
<213> Shewanella putrefaciens

<400> 38
Gly Xaa Gly Xaa Xaa Ala
1 5

<210> 39
<211> 6
<212> PRT
<213> 'Axial Seamount' polynoid polychaete

<400> 39
Gly Xaa Gly Xaa Xaa Pro
1 5

<210> 40
<211> 5
<212> PRT
<213> Shewanella putrefaciens

<400> 40
Gly Xaa Ser Xaa Gly
1 5

<210> 41
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 41
cuacuacuac uaccaagcta aagcacttaa ccgtg 35

<210> 42
<211> 32
<212> DNA
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<220>
<223> Description of Artificial Sequence: synthetic

<400> 42
cuacuacuac uaacagcgaa atgcttatca ag 32

<210> 43
<211> 38
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<400> 43
cuacuacuac uagcgaccaa aaccaaatga gctaatac 38

<210> 44
<211> 12
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<220>
<223> Description of Artificial Sequence: synthetic

<400> 44
aagcccgggc tt 12

<210> 45
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 45
gtacaagccc gggcttagct 20

<210> 46
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 46
cgcgatttaa atggcgcgcc ctgcaggcgg ccgcctgcag ggcgcgccat ttaaat 56

<210> 47
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 47
ctgcagctcg agacaatgtt gatttcctta tacttctgtc c 41

<210> 48
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 48
ggatccagat ctctagctag tcttagctga agctcga 37

<210> 49
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 49
tctagactcg agacaatgag ccagacctct aaacctaca 39

<210> 50
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 50
cccgggctcg agctaattcg cctcactgtc gtttgct 37

<210> 51
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 51
gaattcctcg agacaatgcc gctgcgcatc gcacttatc 39

<210> 52
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 52
ggtaccagat ctttagactt ccccttgaag taaatgg 37

<210> 53
<211> 39
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

<400> 53
gaattcgtcg acacaatgtc attaccagac aatgcttct 39

<210> 54
<211> 38
<212> DNA
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<400> 54
tctagagtcg acttatacag attcttcgat gctgatag 38

<210> 55
<211> 39
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<220>
<223> Description of Artificial Sequence: synthetic

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<210> 56
<211> 37
<212> DNA
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<220>
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<400> 56
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<210> 57
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<220>
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<400> 57
tctagagtcg acacaatggc ggaattagct gttattggt 39

<210> 58
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<212> DNA
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<220>
<223> Description of Artificial Sequence: synthetic

<400> 58
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<210> 59

<211> 42
<212> DNA
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<210> 60
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<223> Description of Artificial Sequence: synthetic

<400> 60
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<210> 61
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<220>
<223> Description of Artificial Sequence: synthetic

<400> 61
cccgggtcga cacaatggct aaaaagaaca ccacatcga 39

<210> 62
<211> 40
<212> DNA
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<220>
<223> Description of Artificial Sequence: synthetic

<400> 62
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<210> 63
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<223> Description of Artificial Sequence: synthetic

<400> 63
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<210> 64
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<400> 64
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<210> 65
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<212> DNA
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<400> 65
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<210> 66
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<400> 66
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<210> 67
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<213> Schizochytrium aggregatum

<400> 67
gtgatgatct ttccctgatg cacgccaagg 30

<210> 68

<211> 30
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<213> Schizochytrium aggregatum

<400> 68
agctcgagac cggcaacccg cagcgccaga 30

<210> 69
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<213> Schizochytrium aggregatum

<400> 69
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ctccgctcca accagtcggg cggtcactcc cagcacaagc acgcccttca gttccacaac 4380
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ttctaa 4446

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35 40 45

Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr Glu
50 55 60

Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val Gln
65 70 75 80

Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg Thr
85 90 95

Arg Thr Val Gly Glu Val Val Asn Ala Met Lys Ala Glu Ile Ala Gly
100 105 110

Gly Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Gly Pro Ala Ala Ala
115 120 125

Ala Pro Ala Pro Ala Val Ser Ser Glu Leu Leu Glu Lys Ala Glu Thr
130 135 140

Val Val Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met
145 150 155 160

Ile Glu Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile
165 170 175

Lys Arg Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu
180 185 190

Ala Lys Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val
195 200 205

Val Asp Ala Met Lys Ala Glu Ile Ala Gly Ser Ser Ala Ser Ala Pro
210 215 220

Ala Ala Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala
225 230 235 240

Ala Ala Pro Ala Val Ser Asn Glu Leu Leu Glu Lys Ala Glu Thr Val
245 250 255

Val Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met Ile

260 265 270

Glu Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile Lys
275 280 285

Arg Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu Ala
290 295 300

Lys Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val Val
305 310 315 320

Asp Ala Met Lys Ala Glu Ile Ala Gly Gly Ser Ala Pro Ala Pro Ala
325 330 335

Ala Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Val Ser Asn Glu
340 345 350

Leu Leu Glu Lys Ala Glu Thr Val Val Met Glu Val Leu Ala Ala Lys
355 360 365

Thr Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr
370 375 380

Glu Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val
385 390 395 400

Gln Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg
405 410 415

Thr Arg Thr Val Gly Glu Val Val Asp Ala Met Lys Ala Glu Ile Ala
420 425 430

Gly Ser Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala
435 440 445

Ala Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Val Ser Ser Glu Leu
450 455 460

Leu Glu Lys Ala Glu Thr Val Val Met Glu Val Leu Ala Ala Lys Thr
465 470 475 480

Gly Tyr Glu Thr Asp Met Ile Glu Ser Asp Met Glu Leu Glu Thr Glu
485 490 495

Leu Gly Ile Asp Ser Ile Lys Arg Val Glu Ile Leu Ser Glu Val Gln
500 505 510

Ala Met Leu Asn Val Glu Ala Lys Asp Val Asp Ala Leu Ser Arg Thr

515 520 525

Arg Thr Val Gly Glu Val Val Asp Ala Met Lys Ala Glu Ile Ala Gly
530 535 540

Gly Ser Ala Pro Ala Pro Ala Ala Ala Ala Pro Ala Pro Ala Ala Ala
545 550 555 560

Ala Pro Ala Val Ser Asn Glu Leu Leu Glu Lys Ala Glu Thr Val Val
565 570 575

Met Glu Val Leu Ala Ala Lys Thr Gly Tyr Glu Thr Asp Met Ile Glu
580 585 590

Ser Asp Met Glu Leu Glu Thr Glu Leu Gly Ile Asp Ser Ile Lys Arg
595 600 605

Val Glu Ile Leu Ser Glu Val Gln Ala Met Leu Asn Val Glu Ala Lys
610 615 620

Asp Val Asp Ala Leu Ser Arg Thr Arg Thr Val Gly Glu Val Val Asp
625 630 635 640

Ala Met Lys Ala Glu Ile Ala Gly Gly Ser Ala Pro Ala Pro Ala Ala
645 650 655

Ala Ala Pro Ala Ser Ala Gly Ala Ala Pro Ala Val Lys Ile Asp Ser
660 665 670

Val His Gly Ala Asp Cys Asp Asp Leu Ser Leu Met His Ala Lys Val
675 680 685

Val Asp Ile Arg Arg Pro Asp Glu Leu Ile Leu Glu Arg Pro Glu Asn
690 695 700

Arg Pro Val Leu Val Val Asp Asp Gly Ser Glu Leu Thr Leu Ala Leu
705 710 715 720

Val Arg Val Leu Gly Ala Cys Ala Val Val Leu Thr Phe Glu Gly Leu
725 730 735

Gln Leu Ala Gln Arg Ala Gly Ala Ala Ala Ile Arg His Val Leu Ala
740 745 750

Lys Asp Leu Ser Ala Glu Ser Ala Glu Lys Ala Ile Lys Glu Ala Glu
755 760 765

Gln Arg Phe Gly Ala Leu Gly Gly Phe Ile Ser Gln Gln Ala Glu Arg

770 775 780

Phe Glu Pro Ala Glu Ile Leu Gly Phe Thr Leu Met Cys Ala Lys Phe
785 790 795 800

Ala Lys Ala Ser Leu Cys Thr Ala Val Ala Gly Gly Arg Pro Ala Phe
805 810 815

Ile Gly Val Ala Arg Leu Asp Gly Arg Leu Gly Phe Thr Ser Gln Gly
820 825 830

Thr Ser Asp Ala Leu Lys Arg Ala Gln Arg Gly Ala Ile Phe Gly Leu
835 840 845

Cys Lys Thr Ile Gly Leu Glu Trp Ser Glu Ser Asp Val Phe Ser Arg
850 855 860

Gly Val Asp Ile Ala Gln Gly Met His Pro Glu Asp Ala Ala Val Ala
865 870 875 880

Ile Val Arg Glu Met Ala Cys Ala Asp Ile Arg Ile Arg Glu Val Gly
885 890 895

Ile Gly Ala Asn Gln Gln Arg Cys Thr Ile Arg Ala Ala Lys Leu Glu
900 905 910

Thr Gly Asn Pro Gln Arg Gln Ile Ala Lys Asp Asp Val Leu Leu Val
915 920 925

Ser Gly Gly Ala Arg Gly Ile Thr Pro Leu Cys Ile Arg Glu Ile Thr
930 935 940

Arg Gln Ile Ala Gly Gly Lys Tyr Ile Leu Leu Gly Arg Ser Lys Val
945 950 955 960

Ser Ala Ser Glu Pro Ala Trp Cys Ala Gly Ile Thr Asp Glu Lys Ala
965 970 975

Val Gln Lys Ala Ala Thr Gln Glu Leu Lys Arg Ala Phe Ser Ala Gly
980 985 990

Glu Gly Pro Lys Pro Thr Pro Arg Ala Val Thr Lys Leu Val Gly Ser
995 1000 1005

Val Leu Gly Ala Arg Glu Val Arg Ser Ser Ile Ala Ala Ile Glu Ala
1010 1015 1020

Leu Gly Gly Lys Ala Ile Tyr Ser Ser Cys Asp Val Asn Ser Ala Ala

1025 1030 1035 1040

Asp Val Ala Lys Ala Val Arg Asp Ala Glu Ser Gln Leu Gly Ala Arg
1045 1050 1055

Val Ser Gly Ile Val His Ala Ser Gly Val Leu Arg Asp Arg Leu Ile
1060 1065 1070

Glu Lys Lys Leu Pro Asp Glu Phe Asp Ala Val Phe Gly Thr Lys Val
1075 1080 1085

Thr Gly Leu Glu Asn Leu Leu Ala Ala Val Asp Arg Ala Asn Leu Lys
1090 1095 1100

His Met Val Leu Phe Ser Ser Leu Ala Gly Phe His Gly Asn Val Gly
1105 1110 1115 1120

Gln Ser Asp Tyr Ala Met Ala Asn Glu Ala Leu Asn Lys Met Gly Leu
1125 1130 1135

Glu Leu Ala Lys Asp Val Ser Val Lys Ser Ile Cys Phe Gly Pro Trp
1140 1145 1150

Asp Gly Gly Met Val Thr Pro Gln Leu Lys Lys Gln Phe Gln Glu Met
1155 1160 1165

Gly Val Gln Ile Ile Pro Arg Glu Gly Gly Ala Asp Thr Val Ala Arg
1170 1175 1180

Ile Val Leu Gly Ser Ser Pro Ala Glu Ile Leu Val Gly Asn Trp Arg
1185 1190 1195 1200

Thr Pro Ser Lys Lys Val Gly Ser Asp Thr Ile Thr Leu His Arg Lys
1205 1210 1215

Ile Ser Ala Lys Ser Asn Pro Phe Leu Glu Asp His Val Ile Gln Gly
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Arg Arg Val Leu Pro Met Thr Leu Ala Ile Gly Ser Leu Ala Glu Thr
1235 1240 1245

Cys Leu Gly Leu Phe Pro Gly Tyr Ser Leu Trp Ala Ile Asp Asp Ala
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Gln Leu Phe Lys Gly Val Thr Val Asp Gly Asp Val Asn Cys Glu Val
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Thr Leu Thr Pro Ser Thr Ala Pro Ser Gly Arg Val Asn Val Gln Ala

1285 1290 1295

Thr Leu Lys Thr Phe Ser Ser Gly Lys Leu Val Pro Ala Tyr Arg Ala
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Val Ile Val Leu Ser Asn Gln Gly Ala Pro Pro Ala Asn Ala Thr Met
1315 1320 1325

Gln Pro Pro Ser Leu Asp Ala Asp Pro Ala Leu Gln Gly Ser Val Tyr
1330 1335 1340

Asp Gly Lys Thr Leu Phe His Gly Pro Ala Phe Arg Gly Ile Asp Asp
1345 1350 1355 1360

Val Leu Ser Cys Thr Lys Ser Gln Leu Val Ala Lys Cys Ser Ala Val
1365 1370 1375

Pro Gly Ser Asp Ala Ala Arg Gly Glu Phe Ala Thr Asp Thr Asp Ala
1380 1385 1390

His Asp Pro Phe Val Asn Asp Leu Ala Phe Gln Ala Met Leu Val Trp
1395 1400 1405

Val Arg Arg Thr Leu Gly Gln Ala Ala Leu Pro Asn Ser Ile Gln Arg
1410 1415 1420

Ile Val Gln His Arg Pro Val Pro Gln Asp Lys Pro Phe Tyr Ile Thr
1425 1430 1435 1440

Leu Arg Ser Asn Gln Ser Gly Gly His Ser Gln His Lys His Ala Leu
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Gln Phe His Asn Glu Gln Gly Asp Leu Phe Ile Asp Val Gln Ala Ser
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Val Ile Ala Thr Asp Ser Leu Ala Phe
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<212> PRT
<213> Schizochytrium aggregatum

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            20   25   30

Arg Ile Ala Ile Thr Gly Met Asp Ala Thr Phe Gly Ala Leu Lys Gly
35 40 45

Leu Asp Ala Phe Glu Arg Ala Ile Tyr Thr Gly Ala His Gly Ala Ile
50 55 60

Pro Leu Pro Glu Lys Arg Trp Arg Phe Leu Gly Lys Asp Lys Asp Phe
65 70 75 80

Leu Asp Leu Cys Gly Val Lys Ala Thr Pro His Gly Cys Tyr Ile Glu
85 90 95

Asp Val Glu Val Asp Phe Gln Arg Leu Arg Thr Pro Met Thr Pro Glu
100 105 110

Asp Met Leu Leu Pro Gln Gln Leu Leu Ala Val Thr Thr Ile Asp Arg
115 120 125

Ala Ile Leu Asp Ser Gly Met Lys Lys Gly Gly Asn Val Ala Val Phe
130 135 140

Val Gly Leu Gly Thr Asp Leu Glu Leu Tyr Arg His Arg Ala Arg Val
145 150 155 160

Ala Leu Lys Glu Arg Val Arg Pro Glu Ala Ser Lys Lys Leu Asn Asp
165 170 175

Met Met Gln Tyr Ile Asn Asp Cys Gly Thr Ser Thr Ser Tyr Thr Ser
180 185 190

Tyr Ile Gly Asn Leu Val Ala Thr Arg Val Ser Ser Gln Trp Gly Phe
195 200 205

Thr Gly Pro Ser Phe Thr Ile Thr Glu Gly Asn Asn Ser Val Tyr Arg
210 215 220

Cys Ala Glu Leu Gly Lys Tyr Leu Leu Glu Thr Gly Glu Val Asp Gly
225 230 235 240

Val Val Val Ala Gly Val Asp Leu Cys Gly Ser Ala Glu Asn Leu Tyr
245 250 255

Val Lys Ser Arg Arg Phe Lys Val Ser Thr Ser Asp Thr Pro Arg Ala
260 265 270

Ser Phe Asp Ala Ala Ala Asp Gly Tyr Phe Val Gly Glu Gly Cys Gly
275 280 285

Ala Phe Val Leu Lys Arg Glu Thr Ser Cys Thr Lys Asp Asp Arg Ile
290 295 300

Tyr Ala Cys Met Asp Ala Ile Val Pro Gly Asn Val Pro Ser Ala Cys
305 310 315 320

Leu Arg Glu Ala Leu Asp Gln Ala Arg Val Lys Pro Gly Asp Ile Glu
325 330 335

Met Leu Glu Leu Ser Ala Asp Ser Ala Arg His Leu Lys Asp Pro Ser
340 345 350

Val Leu Pro Lys Glu Leu Thr Ala Glu Glu Glu Ile Gly Gly Leu Gln
355 360 365

Thr Ile Leu Arg Asp Asp Asp Lys Leu Pro Arg Asn Val Ala Thr Gly
370 375 380

Ser Val Lys Ala Thr Val Gly Asp Thr Gly Tyr Ala Ser Gly Ala Ala
385 390 395 400

Ser Leu Ile Lys Ala Ala Leu Cys Ile Tyr Asn Arg Tyr Leu Pro Ser
405 410 415

Asn Gly Asp Asp Trp Asp Glu Pro Ala Pro Glu Ala Pro Trp Asp Ser
420 425 430

Thr Leu Phe Ala Cys Gln Thr Ser Arg Ala Trp Leu Lys Asn Pro Gly
435 440 445

Glu Arg Arg Tyr Ala Ala Val Ser Gly Val Ser Glu Thr Arg Ser Cys
450 455 460

Tyr Ser Val Leu Leu Ser Glu Ala Glu Gly His Tyr Glu Arg Glu Asn
465 470 475 480

Arg Ile Ser Leu Asp Glu Glu Ala Pro Lys Leu Ile Val Leu Arg Ala
485 490 495

Asp Ser His Glu Glu Ile Leu Gly Arg Leu Asp Lys Ile Arg Glu Arg
500 505 510

Phe Leu Gln Pro Thr Gly Ala Ala Pro Arg Glu Ser Glu Leu Lys Ala
515 520 525

Gln Ala Arg Arg Ile Phe Leu Glu Leu Leu Gly Glu Thr Leu Ala Gln
530 535 540

Asp Ala Ala Ser Ser Gly Ser Gln Lys Pro Leu Ala Leu Ser Leu Val
545 550 555 560

Ser Thr Pro Ser Lys Leu Gln Arg Glu Val Glu Leu Ala Ala Lys Gly
565 570 575

Ile Pro Arg Cys Leu Lys Met Arg Arg Asp Trp Ser Ser Pro Ala Gly
580 585 590

Ser Arg Tyr Ala Pro Glu Pro Leu Ala Ser Asp Arg Val Ala Phe Met
595 600 605

Tyr Gly Glu Gly Arg Ser Pro Tyr Tyr Gly Ile Thr Gln Asp Ile His
610 615 620

Arg Ile Trp Pro Glu Leu His Glu Val Ile Asn Glu Lys Thr Asn Arg
625 630 635 640

Leu Trp Ala Glu Gly Asp Arg Trp Val Met Pro Arg Ala Ser Phe Lys
645 650 655

Ser Glu Leu Glu Ser Gln Gln Gln Glu Phe Asp Arg Asn Met Ile Glu
660 665 670

Met Phe Arg Leu Gly Ile Leu Thr Ser Ile Ala Phe Thr Asn Leu Ala
675 680 685

Arg Asp Val Leu Asn Ile Thr Pro Lys Ala Ala Phe Gly Leu Ser Leu
690 695 700

Gly Glu Ile Ser Met Ile Phe Ala Phe Ser Lys Lys Asn Gly Leu Ile
705 710 715 720

Ser Asp Gln Leu Thr Lys Asp Leu Arg Glu Ser Asp Val Trp Asn Lys
725 730 735

Ala Leu Ala Val Glu Phe Asn Ala Leu Arg Glu Ala Trp Gly Ile Pro
740 745 750

Gln Ser Val Pro Lys Asp Glu Phe Trp Gln Gly Tyr Ile Val Arg Gly
755 760 765

Thr Lys Gln Asp Ile Glu Ala Ala Ile Ala Pro Asp Ser Lys Tyr Val
770 775 780

Arg Leu Thr Ile Ile Asn Asp Ala Asn Thr Ala Leu Ile Ser Gly Lys
785 790 795 800

Pro Asp Ala Cys Lys Ala Ala Ile Ala Arg Leu Gly Gly Asn Ile Pro
805 810 815

Ala Leu Pro Val Thr Gln Gly Met Cys Gly His Cys Pro Glu Val Gly
820 825 830

Pro Tyr Thr Lys Asp Ile Ala Lys Ile His Ala Asn Leu Glu Phe Pro
835 840 845

Val Val Asp Gly Leu Asp Leu Trp Thr Thr Ile Asn Gln Lys Arg Leu
850 855 860

Val Pro Arg Ala Thr Gly Ala Lys Asp Glu Trp Ala Pro Ser Ser Phe
865 870 875 880

Gly Glu Tyr Ala Gly Gln Leu Tyr Glu Lys Gln Ala Asn Phe Pro Gln
885 890 895

Ile Val Glu Thr Ile Tyr Lys Gln Asn Tyr Asp Val Phe Val Glu Val
900 905 910

Gly Pro Asn Asn His Arg Ser Thr Ala Val Arg Thr Thr Leu Gly Pro
915 920 925

Gln Arg Asn His Leu Ala Gly Ala Ile Asp Lys Gln Asn Glu Asp Ala
930 935 940

Trp Thr Thr Ile Val Lys Leu Val Ala Ser Leu Lys Ala His Leu Val
945 950 955 960

Pro Gly Val Thr Ile Ser Pro Leu Tyr His Ser Lys Leu Val Ala Glu
965 970 975

Ala Gln Ala Cys Tyr Ala Ala Leu Cys Lys Gly Glu Lys Pro Lys Lys
980 985 990

Asn Lys Phe Val Arg Lys Ile Gln Leu Asn Gly Arg Phe Asn Ser Lys
995 1000 1005

Ala Asp Pro Ile Ser Ser Ala Asp Leu Ala Ser Phe Pro Pro Ala Asp
1010 1015 1020

Pro Ala Ile Glu Ala Ala Ile Ser Ser Arg Ile Met Lys Pro Val Ala
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Pro Lys Phe Tyr Ala Arg Leu Asn Ile Asp Glu Gln Asp Glu Thr Arg
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Asp Pro Ile Leu Asn Lys Asp Asn Ala Pro Ser Ser Ser Ser Ser Ser
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1075 1080 1085

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Ala Leu Ser Ser Ala Ser Ala Ser Gly Asn Leu Val Glu Thr Ala Pro
1125 1130 1135

Ser Asp Ala Ser Val Ile Val Pro Pro Cys Asn Ile Ala Asp Leu Gly
1140 1145 1150

Ser Arg Ala Phe Met Lys Thr Tyr Gly Val Ser Ala Pro Leu Tyr Thr
1155 1160 1165

Gly Ala Met Ala Lys Gly Ile Ala Ser Ala Asp Leu Val Ile Ala Ala
1170 1175 1180

Gly Arg Gln Gly Ile Leu Ala Ser Phe Gly Ala Gly Gly Leu Pro Met
1185 1190 1195 1200

Gln Val Val Arg Glu Ser Ile Glu Lys Ile Gln Ala Ala Leu Pro Asn
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Gly Pro Tyr Ala Val Asn Leu Ile His Ser Pro Phe Asp Ser Asn Leu
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Glu Lys Gly Asn Val Asp Leu Phe Leu Glu Lys Gly Val Thr Phe Val
1235 1240 1245

Glu Ala Ser Ala Phe Met Thr Leu Thr Pro Gln Val Val Arg Tyr Arg
1250 1255 1260

Ala Ala Gly Leu Thr Arg Asn Ala Asp Gly Ser Val Asn Ile Arg Asn
1265 1270 1275 1280

Arg Ile Ile Gly Lys Val Ser Arg Thr Glu Leu Ala Glu Met Phe Met
1285 1290 1295

Arg Pro Ala Pro Glu His Leu Leu Gln Lys Leu Ile Ala Ser Gly Glu
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Ile Asn Gln Glu Gln Ala Glu Leu Ala Arg Arg Val Pro Val Ala Asp
1315 1320 1325

Asp Ile Ala Val Glu Ala Asp Ser Gly Gly His Thr Asp Asn Arg Pro
1330 1335 1340

Ile His Val Ile Leu Pro Leu Ile Ile Asn Leu Arg Asp Arg Leu His
1345 1350 1355 1360

Arg Glu Cys Gly Tyr Pro Ala Asn Leu Arg Val Arg Val Gly Ala Gly
1365 1370 1375

Gly Gly Ile Gly Cys Pro Gln Ala Ala Leu Ala Thr Phe Asn Met Gly
1380 1385 1390

Ala Ser Phe Ile Val Thr Gly Thr Val Asn Gln Val Ala Lys Gln Ser
1395 1400 1405

Gly Thr Cys Asp Asn Val Arg Lys Gln Leu Ala Lys Ala Thr Tyr Ser
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Asp Val Cys Met Ala Pro Ala Ala Asp Met Phe Glu Glu Gly Val Lys
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Leu Gln Val Leu Lys Lys Gly Thr Met Phe Pro Ser Arg Ala Asn Lys
1445 1450 1455

Leu Tyr Glu Leu Phe Cys Lys Tyr Asp Ser Phe Glu Ser Met Pro Pro
1460 1465 1470

Ala Glu Leu Ala Arg Val Glu Lys Arg Ile Phe Ser Arg Ala Leu Glu
1475 1480 1485

Glu Val Trp Asp Glu Thr Lys Asn Phe Tyr Ile Asn Arg Leu His Asn
1490 1495 1500

Pro Glu Lys Ile Gln Arg Ala Glu Arg Asp Pro Lys Leu Lys Met Ser
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Leu Cys Phe Arg Trp Tyr Leu Ser Leu Ala Ser Arg Trp Ala Asn Thr
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Gly Ala Ser Asp Arg Val Met Asp Tyr Gln Val Trp Cys Gly Pro Ala
1540 1545 1550

Ile Gly Ser Phe Asn Asp Phe Ile Lys Gly Thr Tyr Leu Asp Pro Ala
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Val Ala Asn Glu Tyr Pro Cys Val Val Gln Ile Asn Lys Gln Ile Leu
1570 1575 1580

Arg Gly Ala Cys Phe Leu Arg Arg Leu Glu Ile Leu Arg Asn Ala Arg
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Val Pro Ala Glu Lys Leu
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Gln Gln Gln Gln Pro Arg Glu Gly Asp Lys Glu Lys Ala Ala Glu Thr
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Met Ala Leu Arg Val Lys Thr Asn Lys Lys Pro Cys Trp Glu Met Thr
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Lys Glu Glu Leu Thr Ser Gly Lys Thr Glu Val Phe Asn Tyr Glu Glu
65 70 75 80

Leu Leu Glu Phe Ala Glu Gly Asp Ile Ala Lys Val Phe Gly Pro Glu
85 90 95

Phe Ala Val Ile Asp Lys Tyr Pro Arg Arg Val Arg Leu Pro Ala Arg
100 105 110

Glu Tyr Leu Leu Val Thr Arg Val Thr Leu Met Asp Ala Glu Val Asn
115 120 125

Asn Tyr Arg Val Gly Ala Arg Met Val Thr Glu Tyr Asp Leu Pro Val
130 135 140

Asn Gly Glu Leu Ser Glu Gly Gly Asp Cys Pro Trp Ala Val Leu Val

145 150 155 160

Glu Ser Gly Gln Cys Asp Leu Met Leu Ile Ser Tyr Met Gly Ile Asp
165 170 175

Phe Gln Asn Gln Gly Asp Arg Val Tyr Arg Leu Leu Asn Thr Thr Leu
180 185 190

Thr Phe Tyr Gly Val Ala His Glu Gly Glu Thr Leu Glu Tyr Asp Ile
195 200 205

Arg Val Thr Gly Phe Ala Lys Arg Leu Asp Gly Gly Ile Ser Met Phe
210 215 220

Phe Phe Glu Tyr Asp Cys Tyr Val Asn Gly Arg Leu Leu Ile Glu Met
225 230 235 240

Arg Asp Gly Cys Ala Gly Phe Phe Thr Asn Glu Glu Leu Asp Ala Gly
245 250 255

Lys Gly Val Val Phe Thr Arg Gly Asp Leu Ala Ala Arg Ala Lys Ile
260 265 270

Pro Lys Gln Asp Val Ser Pro Tyr Ala Val Ala Pro Cys Leu His Lys
275 280 285

Thr Lys Leu Asn Glu Lys Glu Met Gln Thr Leu Val Asp Lys Asp Trp
290 295 300

Ala Ser Val Phe Gly Ser Lys Asn Gly Met Pro Glu Ile Asn Tyr Lys
305 310 315 320

Leu Cys Ala Arg Lys Met Leu Met Ile Asp Arg Val Thr Ser Ile Asp
325 330 335

His Lys Gly Gly Val Tyr Gly Leu Gly Gln Leu Val Gly Glu Lys Ile
340 345 350

Leu Glu Arg Asp His Trp Tyr Phe Pro Cys His Phe Val Lys Asp Gln
355 360 365

Val Met Ala Gly Ser Leu Val Ser Asp Gly Cys Ser Gln Met Leu Lys
370 375 380

Met Tyr Met Ile Trp Leu Gly Leu His Leu Thr Thr Gly Pro Phe Asp
385 390 395 400

Phe Arg Pro Val Asn Gly His Pro Asn Lys Val Arg Cys Arg Gly Gln

405 410 415

Ile Ser Pro His Lys Gly Lys Leu Val Tyr Val Met Glu Ile Lys Glu
420 425 430

Met Gly Phe Asp Glu Asp Asn Asp Pro Tyr Ala Ile Ala Asp Val Asn
435 440 445

Ile Ile Asp Val Asp Phe Glu Lys Gly Gln Asp Phe Ser Leu Asp Arg
450 455 460

Ile Ser Asp Tyr Gly Lys Gly Asp Leu Asn Lys Lys Ile Val Val Asp
465 470 475 480

Phe Lys Gly Ile Ala Leu Lys Met Gln Lys Arg Ser Thr Asn Lys Asn
485 490 495

Pro Ser Lys Val Gln Pro Val Phe Ala Asn Gly Ala Ala Thr Val Gly
500 505 510

Pro Glu Ala Ser Lys Ala Ser Ser Gly Ala Ser Ala Ser Ala Ser Ala
515 520 525

Ala Pro Ala Lys Pro Ala Phe Ser Ala Asp Val Leu Ala Pro Lys Pro
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Val Ala Leu Pro Glu His Ile Leu Lys Gly Asp Ala Leu Ala Pro Lys
545 550 555 560

Glu Met Ser Trp His Pro Met Ala Arg Ile Pro Gly Asn Pro Thr Pro
565 570 575

Ser Phe Ala Pro Ser Ala Tyr Lys Pro Arg Asn Ile Ala Phe Thr Pro
580 585 590

Phe Pro Gly Asn Pro Asn Asp Asn Asp His Thr Pro Gly Lys Met Pro
595 600 605

Leu Thr Trp Phe Asn Met Ala Glu Phe Met Ala Gly Lys Val Ser Met
610 615 620

Cys Leu Gly Pro Glu Phe Ala Lys Phe Asp Asp Ser Asn Thr Ser Arg
625 630 635 640

Ser Pro Ala Trp Asp Leu Ala Leu Val Thr Arg Ala Val Ser Val Ser
645 650 655

Asp Leu Lys His Val Asn Tyr Arg Asn Ile Asp Leu Asp Pro Ser Lys

660 665 670

Gly Thr Met Val Gly Glu Phe Asp Cys Pro Ala Asp Ala Trp Phe Tyr
675 680 685

Lys Gly Ala Cys Asn Asp Ala His Met Pro Tyr Ser Ile Leu Met Glu
690 695 700

Ile Ala Leu Gln Thr Ser Gly Val Leu Thr Ser Val Leu Lys Ala Pro
705 710 715 720

Leu Thr Met Glu Lys Asp Asp Ile Leu Phe Arg Asn Leu Asp Ala Asn
725 730 735

Ala Glu Phe Val Arg Ala Asp Leu Asp Tyr Arg Gly Lys Thr Ile Arg
740 745 750

Asn Val Thr Lys Cys Thr Gly Tyr Ser Met Leu Gly Glu Met Gly Val
755 760 765

His Arg Phe Thr Phe Glu Leu Tyr Val Asp Asp Val Leu Phe Tyr Lys
770 775 780

Gly Ser Thr Ser Phe Gly Trp Phe Val Pro Glu Val Phe Ala Ala Gln
785 790 795 800

Ala Gly Leu Asp Asn Gly Arg Lys Ser Glu Pro Trp Phe Ile Glu Asn
805 810 815

Lys Val Pro Ala Ser Gln Val Ser Ser Phe Asp Val Arg Pro Asn Gly
820 825 830

Ser Gly Arg Thr Ala Ile Phe Ala Asn Ala Pro Ser Gly Ala Gln Leu
835 840 845

Asn Arg Arg Thr Asp Gln Gly Gln Tyr Leu Asp Ala Val Asp Ile Val
850 855 860

Ser Gly Ser Gly Lys Lys Ser Leu Gly Tyr Ala His Gly Ser Lys Thr
865 870 875 880

Val Asn Pro Asn Asp Trp Phe Phe Ser Cys His Phe Trp Phe Asp Ser
885 890 895

Val Met Pro Gly Ser Leu Gly Val Glu Ser Met Phe Gln Leu Val Glu
900 905 910

Ala Ile Ala Ala His Glu Asp Leu Ala Gly Lys Ala Arg His Cys Gln

915 920 925

Pro His Leu Cys Ala Arg Pro Arg Ala Arg Ser Ser Trp Lys Tyr Arg
930 935 940

Gly Gln Leu Thr Pro Lys Ser Lys Lys Met Asp Ser Glu Val His Ile
945 950 955 960

Val Ser Val Asp Ala His Asp Gly Val Val Asp Leu Val Ala Asp Gly
965 970 975

Phe Leu Trp Ala Asp Ser Leu Arg Val Tyr Ser Val Ser Asn Ile Arg
980 985 990

Val Arg Ile Ala Ser Gly Glu Ala Pro Ala Ala Ala Ser Ser Ala Ala
995 1000 1005

Ser Val Gly Ser Ser Ala Ser Ser Val Glu Arg Thr Arg Ser Ser Pro
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Ala Val Ala Ser Gly Pro Ala Gln Thr Ile Asp Leu Lys Gln Leu Lys
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Thr Glu Leu Leu Glu Leu Asp Ala Pro Leu Tyr Leu Ser Gln Asp Pro
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Thr Ser Gly Gln Leu Lys Lys His Thr Asp Val Ala Ser Gly Gln Ala
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Thr Ile Val Gln Pro Cys Thr Leu Gly Asp Leu Gly Asp Arg Ser Phe
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Met Glu Thr Tyr Gly Val Val Ala Pro Leu Tyr Thr Gly Ala Met Ala
1090 1095 1100

Lys Gly Ile Ala Ser Ala Asp Leu Val Ile Ala Ala Gly Lys Arg Lys
1105 1110 1115 1120

Ile Leu Gly Ser Phe Gly Ala Gly Gly Leu Pro Met His His Val Arg
1125 1130 1135

Ala Ala Leu Glu Lys Ile Gln Ala Ala Leu Pro Gln Gly Pro Tyr Ala
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Val Asn Leu Ile His Ser Pro Phe Asp Ser Asn Leu Glu Lys Gly Asn
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Val Asp Leu Phe Leu Glu Lys Gly Val Thr Val Val Glu Ala Ser Ala

1170 1175 1180

Phe Met Thr Leu Thr Pro Gln Val Val Arg Tyr Arg Ala Ala Gly Leu
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Ser Arg Asn Ala Asp Gly Ser Val Asn Ile Arg Asn Arg Ile Ile Gly
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Lys Val Ser Arg Thr Glu Leu Ala Glu Met Phe Ile Arg Pro Ala Pro
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Glu His Leu Leu Glu Lys Leu Ile Ala Ser Gly Glu Ile Thr Gln Glu
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Gln Ala Glu Leu Ala Arg Arg Val Pro Val Ala Asp Asp Ile Ala Val
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Glu Ala Asp Ser Gly Gly His Thr Asp Asn Arg Pro Ile His Val Ile
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Leu Pro Leu Ile Ile Asn Leu Arg Asn Arg Leu His Arg Glu Cys Gly
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Tyr Pro Ala His Leu Arg Val Arg Val Gly Ala Gly Gly Gly Val Gly
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Cys Pro Gln Ala Ala Ala Ala Ala Leu Thr Met Gly Ala Ala Phe Ile
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Val Thr Gly Thr Val Asn Gln Val Ala Lys Gln Ser Gly Thr Cys Asp
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Asn Val Arg Lys Gln Leu Ser Gln Ala Thr Tyr Ser Asp Ile Cys Met
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Ala Pro Ala Ala Asp Met Phe Glu Glu Gly Val Lys Leu Gln Val Leu
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Lys Lys Gly Thr Met Phe Pro Ser Arg Ala Asn Lys Leu Tyr Glu Leu
1380 1385 1390

Phe Cys Lys Tyr Asp Ser Phe Asp Ser Met Pro Pro Ala Glu Leu Glu
1395 1400 1405

Arg Ile Glu Lys Arg Ile Phe Lys Arg Ala Leu Gln Glu Val Trp Glu
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Glu Thr Lys Asp Phe Tyr Ile Asn Gly Leu Lys Asn Pro Glu Lys Ile

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Gln Arg Ala Glu His Asp Pro Lys Leu Lys Met Ser Leu Cys Phe Arg
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Trp Tyr Leu Gly Leu Ala Ser Arg Trp Ala Asn Met Gly Ala Pro Asp
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Arg Val Met Asp Tyr Gln Val Trp Cys Gly Pro Ala Ile Gly Ala Phe
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Asn Asp Phe Ile Lys Gly Thr Tyr Leu Asp Pro Ala Val Ser Asn Glu
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Tyr Pro Cys Val Val Gln Ile Asn Leu Gln Ile Leu Arg Gly Ala Cys
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<211> 1665

<212> DNA

<213> Vibrio marinus

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<212> DNA
<213> Shewanella putrefaciens

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<212> DNA
<213> Shewanella putrefaciens

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<212> DNA
<213> Shewanella putrefaciens

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